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(54)REMEDIES OR PREVENTIVES FOR DISEASES IN ASSOCIATION WITH CHEMOKINES

This invention provides remedies or prophylac-(57)tics for diseases in association with chemokines such as MIP-1 α and/or MCP-1. Namely, remedies or prophylactics for diseases in association with the chemokines such as rheumatoid arthritis or nephritis contain, as the

active ingredient, cyclic amine derivatives represented by the following formula (I), pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable C₁-C₆ alkyl addition salts thereof.

Description

Technical Field

5 [0001] The present invention relates to cyclic amine derivatives and more particularly it relates to chemokine receptor antagonists capable of expecting effects as remedies and/or prophylactics for diseases such as atherosclerosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, nephritis (nephropathy), multiple sclerosis, pulmonary fibrosis, cardiomyopathy, hepatitis, pancreatitis, sarcoidosis, Crohn's disease, endometriosis, congestive heart failure, viral meningitis, cerebral infarction, neuropathy, Kawasaki disease, sepsis, allergic rhinitis and allergic dematitis wherein infiltration of blood leukocyte components such as monocytes or lymphocytes into tissues plays a principal role in progression and maintenance of diseases.

Background Art

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- [0002] Chemokines are a generic name of a group of inflammatory/immunomodulatory polypeptides having a molecular weight of 6 to 15 KD and produced in inflammatory sites by various kinds of cells, for example, macrophages, monocytes, eosinophils, neutrophils, fibroblasts, vascular endothelial cells, smooth muscle cells and mast cells. The chemokines are classified into two major subgroups of CXC chemokines (or α-chemokines) and CC chemokines (or β-chemokines) by the common location of four preserved cysteine residues and a difference in chromosomal locations of genes encoding the chemokines. The first two cysteines of the CXC chemokines are separated by one amino acid; however, the same cysteines of the CC chemokine are adjacent. For example, IL-8 (an abbreviation for interleukin 8) is the CXC chemokines. On the other hand, MIP-1 α/β (an abbreviation for macrophage inflammatory protein-1 α/β), MCP-1 (an abbreviation for monocyte chemoattractant protein-1) and RANTES (an abbreviation for regulated upon activation, normal T-cell expressed and secreted) are cited as the CC chemokines.
- [0003] Furthermore, there also exist chemokines which do not fall into either of chemokine subgroups. Lymphotactin having only two cysteines and classified as C chemokines and fractalkine classified as CX3C chemokines because the first two cysteines are separated by three amino acids and having a chemokinelike domain in the mucin structure are cited as such a chemokine. The chemokines promote cell migration and have expression enhancing actions on cellular adhesion molecules such as integrins and further cellular adhesion enhancing actions. Therefore, the chemokines are thought to be protein factors closely involved in the adhesion and infiltration of leukocytes or the like into the pathogenic sites such as inflammatory tissues. See, for example, The Chemokine Facts Book, by Vaddi, K. et al., Academic Press, 1997; Chemoattractant Ligand and Their Receptors, edited by Horuk, R., CRC Press, 1996; Ward, G. W. et al., Biochem. J., 1998, 333, 457; Luster, A. D., New Engl. J. Med., 1998, 338, 436; Bagglioni, M., Nature, 1998, 392, 565; Rollins. B. J., Blood, 1997, 90, 909; Alam, R., J. Allergy Clin. Immunol., 1997, 99, 273; Hancock, W. W., Am. J. Pathol., 1996, 148, 681; Taub, D. D., Cytokine & Growth Factor Rev., 1996, 7, 335; Strieter, R. M. et al., J. Immunol., 1996, 156, 3583; Furie, M. B. et al., Am. J. Pathol., 1995, 146, 1287; Schall, T. J. et al., Current Opinion in Immunology, 1994, 6, 865,; and Edginton, S. M., Biotechnology, 1993, 11, 676 as references.
 - [0004] For example, MIP-1 α causes a transient increase in intracellular calcium ion concentration levels and induces cell migration of T lymphocytes or B lymphocytes (see, for example, Tabu, D. D. et al., Science, 1993, 260, 355 and Shall, T. J. et al., J. Exp. Med., 1993, 177, 1821), cell migration of eosinophils (see, for example, Rot, A. et al., J. Exp. Med., 1992, 176, 1489), cell migration of NK cells (see, for example, Magazachi, A. A. et al., J. Immunol., 1994, 153, 4969), expression of integrins (see, for example, Vaddi, K. et al., J. Immunol., 1994, 153, 4721) and differentiation of osteoclasts (see, for example, Kukita, T. et al., Lab. Invest., 1997, 76, 399). MIP-1 α also increases the IgE and IgG4 production in B cells (see, for example, Kimata, H. et al., J. Exp. Med., 1996, 183, 2397) and inhibits the proliferation of hematopoietic stem cells (see, for example, Mayani, H. et al., Exp. Hematol., 1995, 23, 422; Keller, J. R. et al., Blood, 1994, 84, 2175; Eaves, C. J. et al., Proc. Natl. Acad. Sci. USA, 1993, 90, 12015; Bodine, D. M. et al., Blood, 1991, 78, 914; and Broxmeyer, H. E. et al., Blood, 1990, 76, 1110).
 - [0005] As to the association of MIP-1 α with in vivo actions or pathogenesis of diseases, it has been reported that the MIP-1 α is a pyrogen in rabbits (see, for example, Davatelis, G. et al., Science, 1989, 243, 1066) and the injection of the MIP-1 α into the footpads of mice results in inflammatory reactions such as infiltration of neutrophils or mononuclear cells (see, for example, Alam, R. et al., J. Immunol., 1994, 152, 1298).
 - [0006] It has been also reported that a neutralizing antibody to MIP-1α has inhibitory effects or remedial effects in animal models of granuloma (see, for example, Lukacs, N. W. et al., J. Exp. Med., 1993, 177, 1551), asthma (see, for example, Lukacs, N. W. et al., J. Immunol., 1995, 25, 245 and Lukacs, N. W. et al., J. Immunol., 1997, 158, 4398), multiple sclerosis (see, for example, Karpus, W. J. et al., J. Immunol., 1995, 155, 5003 and Karpus, W. J. et al., J. Leukoc. Biol., 1997, 62, 681), idiopathic pulmonary fibrosis (see, for example, Smith, R. E. et al., J. Immunol., 1994, 153, 4704 and Smith, R. E., Biol. Signals, 1996, 5, 223), acute lung injury (see, for example, Shanley, T. P. et al., J. Immunol., 1995, 154, 4793 and Standiford, T. J. et al., J. Immunol., 1995, 155, 1515) and rheumatoid arthritis (see, for

example, Kasama, T. et al., J. Clin. Invest., 1995, 95, 2868) and the like. Furthermore, it has been reported that coxsackie virus infection-induced myocarditis or herpes stromal keratitis is inhibited in MIP-1α gene deficient mice (see, for example, Cook, D. N. et al., Science, 1995, 269, 1583 and Tumpey, T. M. et al., J. Virology, 1998, 72, 3705).

[0007] In addition, significant expression of MIP-1 α was recognized in patients such as chronic pulmonary inflammatory diseases (see, for example, Standiford, T. J. et al., J. Immunol., 1993, 151, 2852), hypersensitivity pneumonitis (see, for example, Denis, M., Am. J. Respir. Crit. Care Med., 1995, 151, 164), rheumatoid arthritis (see, for example, Koch, A. E. et al., J. Clin. Invest., 1994, 93, 921), infectious meningitis (see, for example, Lahrtz, F. et al., J. Neuroimmunol., 1998, 85, 33) and chronic inflammation of muscle (see, for example, Adams, E. M. et al., Proc. Assoc. Am. Physicians, 1997, 109, 275). The studies indicate that MIP-1 α is deeply involved in the local accumulation of various subtypes of leukocytes in association with initiation, progression and maintenance of inflammatory diseases.

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[0008] MCP-1 [also known as MCAF (an abbreviation for macrophage chemotactic and activating factor) or JE] is a CC chemokine produced by monocytes/macrophages, smooth muscle cells, fibroblasts and vascular endothelial cells and has a cell migration activity and cell adhesion enhancing actions on monocytes (see, for example, Valente, A. J. et al., Biochemistry, 1988, 27, 4162; Matsushima, K. et al., J. Exp. Med., 1989, 169, 1485; Yoshimura, T. et al., J. Immunol., 1989, 142, 1956; Rollins, B. J. et al., Proc. Natl. Acad. Sci. USA, 1988, 85, 3738; Rollins, B. J. et al., Blood, 1991, 78, 1112; Jiang, Y. et al., J. Immunol., 1992, 148, 2423; and Vaddi, K. et al., J. Immunol., 1994, 153, 4721), memory Tlymphocytes (see, for example, Carr., M. W. et al., Proc. Natl. Acad. Sci. USA, 1994, 91, 3652), Tlymphocytes (see, for example, Loetscher, P. et al., FASEB J., 1994, 8, 1055) and natural killer cells (NK cells) (see, for example, Loetscher, P. et al., J. Immunol., 1996, 156, 322 and Allavena, P. et al., Eur. J. Immunol., 1994, 24, 3233) or the like and MCP-1 further has actions as a histamine releasing factor from basophils (see, for example, Alam R. et al., J. Clin. Invest., 1992, 89, 723; Bischoff, S. C. et al., J. Exp. Med., 1992, 175, 1271; and Kuna, P. et al., J. Exp. Med., 1992, 175, 489).

[0009] Moreover, remarkable expression of MCP-1 has been reported in diseases in which the accumulation of monocytes/macrophages and/or T cells is thought to be deeply involved in initiation, progression and maintenance of lesions such as atherosclerosis (see, for example, Hayes, I. M. et al., Arterioscler. Thromb, Vasc. Biol., 1998, 18, 397; Takeya, M. et al., Hum. Pathol., 1993, 24, 534; Yla-Herttuala, S. et al., Proc. Natl. Acad. Sci. USA, 1991, 88, 5252; and Nelken, N. A., J. Clin. Invest., 1991, 88, 1121), rheumatoid arthritis (see, for example, Koch, A. E. et al., J. Clin. Invest., 1992, 90, 772; Akahoshi, T. et al., Arthritis Rheum., 1993. 36, 762; and Robinson, E. et al., Clin. Exp. Immunol., 101, 398), nephritis (see, for example, Noris, M. et al., Lab. Invest., 1995, 73, 804; Wada, T. et al., Kidney Int., 1996, 49, 761; and Gesualdo, L. et al., Kidney Int., 1997, 51, 155), nephropathy (see, for example, Saitoh, A. et al., J. Clin. Lab. Anal., 1998, 12, 1; Yokoyama, H. et al., J. Leukoc. Biol., 1998, 63, 493), pulmonary fibrosis and pulmonary sarcoidosis (see, for example, Sugiyama, Y. et al., Internal Medicine, 1997, 36, 856), asthma (see, for example, Karina, M. et al., J. Invest. Allergol. Clin. Immunol., 1997, 7, 254; Stephene, T. H., Am. J. Respir. Crit. Care Med., 1997, 156, 1377; and Sousa, A. R. et al., Am. J. Respir. Cell Mol. Biol., 1994, 10, 142), multiple sclerosis (see, for example, McManus, C. et al., J. Neuroimmunol., 1998, 86, 20), psoriasis (see, for example, Gillitzer, R. et al., J. Invest. Dermatol., 1993. 101, 127), inflammatory bowel disease (see, for example, Grimm, M. C. et al., J. Leukoc. Biol., 1996, 59, 804 and Reinecker, H. C. et al., Gastroenterology, 1995, 106, 40), cardiomyopathy (see, for example, Seino, Y. et al., Cytokine, 1995, 7, 301), endometriosis (see, for example, Jolicoeur, C. et al., Am. J. Pathol., 1998, 152, 125), intraperitoneal adhesion (see, for example, Zeyneloglu, H. B. et al., Human Reproduction, 1998, 13, 1194), congestive heart failure (see, for example, Aurust, P. et al., Circulation, 1998, 97, 1136), chronic liver disease (see, for example, Marra, F. et al., Am. J. Pathol., 1998, 152, 423), viral meningitis (see, for example, Lahrtz, F. et al., Eur. J. Immunol., 1997, 27, 2484), Kawasaki disease (see, for example, Wong, M. et al., J. Rheumatol., 1997, 24, 1179) and sepsis (see, for example, Salkowski, C. A. et al., Infect. Immun., 1998, 66, 3569).

[0010] The inhibitory effects or remedial effects of an anti-MCP-1 antibody have been reported in animal models such as rheumatoid arthritis (see, for example, Schimmer, R. C. et al., J. Immunol., 1998, 160, 1466; Schrier, D. J., J. Leukoc. Biol., 1998, 63, 359; and Ogata H. et al., J. Pathol., 1997, 182, 106), multiple sclerosis (see, for example, Karpus, W. J., J. Leukoc. Biol., 1997, 62., 681), nephritis (see, for example, Lloyd, C. M. et al., J. Exp. Med., 1997, 185, 1371 and Wada T. et al., FASEB J., 1996, 10, 1418), asthma (see, for example, Gonzalo, J.-A. et al., J. Exp. Med., 1998, 188, 157 and Lukacs, N. W., J. Immunol., 1997, 158, 4398), atherosclerosis (see, for example, Guzman, L. A. et al., Circulation, 1993, 88 (suppl.), I-371), delayed type hypersensitivity (see, for example, Rand, M. L. et al., Am. J. Pathol., 1996, 148, 855), pulmonary hypertension (see, for example, Kimura, H. et al., Lab. Invest., 1998, 78, 571) and intraperitoneal adhesion (see, for example, Zeyneloglu, H. B. et al., Am. J. Obstet. Gynecol., 1998, 179, 438).

[0011] Further, it has been reported that MCP-1 (9-76) which is a peptide antagonist of MCP-1 inhibits arthritis in the mouse model (see, for example, Gong, J.-H., J. Exp. Med., 1997, 186, 131) and that MCP-1 is essential to monocyte mobilization in vivo in studies on MCP-1 gene deficient mice (see, for example, Lu, B. et al., J. Exp. Med., 1998, 187, 601 and Gu, L. et al., Moll. Cell, 1998, 2, 275).

[0012] These data indicate that chemokines such as MIP-1 α and MCP-1 accumulate monocytes, lymphocytes or the like in disease sites and activate the cells and thus strongly suggest that the chemokines are deeply associated

with initiation, progression and maintenance of diseases wherein monocytes, lymphocytes and the like are assumed to be deeply associated with the progression of lesion, for example, atherosclerosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, nephritis (nephropathy), multiple sclerosis, pulmonary fibrosis, myocarditis, hepatitis, pancreatitis, sarcoidosis, Crohn's disease, endometriosis, congestive heart failure, viral meningitis, cerebral infarction, neuropathy, Kawasaki disease and sepsis (see, for example, Rovin, B. H. et al., Am. J. Kidney. Dis., 1998, 31, 1065; Lloyd, C. et al., Curr. Opin. Nephrol. Hypertens., 1998, 7, 281; Conti, P. et al., Allergy and Asthma Proc., 1998, 19, 121; Ransohoff, R. M. et al., Trends Neuroscience., 1998, 21, 154; and MacDermott, R. P. et al., Inflammatory Bowel Diseases, 1998, 4, 54). A drug which inhibits actions of chemokines on target cells, therefore, can be expected to be useful as remedies and/or prophylactics for the diseases.

[0013] On the other hand, the cloning of genes encoding specific receptors for chemokines has been promoted, and it has become apparent that the receptors are G protein-coupled seven-transmembrane receptors present on various leukocytes. At least 5 CXC chemokine receptors (CXCR1 to CXCR5) and eight CC chemokine receptors (CCR1 to CCR8) have hitherto been specified. For example, IL-8 is a ligand of CXCR1 and CXCR2. MIP-1α is a ligand of CCR1 and CCR5, and MCP-1 is a ligand of CCR2A and CCR2B (see, for example, Holmes, W. E. et al., Science, 1991, 253, 1278-1280; Murphy, P. M. et al., Science, 253, 1280-1283; Neote, K. et al., Cell, 1993, 72, 415-425; Charo, I. F. et al., Proc. Natl. Acad. Sci., USA, 1994, 91, 2752-2756; Yamagami, S. et al., Biochem. Biophys. Res. Commun., 1994, 202, 1156-1162; Combadier, C. et al., The Journal of Biological Chemistry, 1995, 270, 16491-16494; Power, C. A. et al., J. Biol. Chem., 1995, 270, 19495-19500; Samson, M. et al., Biohemistry, 1996, 35, 3362-3367; and Murphy, P. M. et al., Annual Review of Immunology, 1994, 12, 592-633).

[0014] Further, it has been reported that the pulmonary inflammation and granuloma are suppressed in CCR1 gene deficient mice (see, for example, Gao, J.-L. et al., J. Exp. Med., 1997, 185, 1959 and Gerard, C. et al., J. Clin. Invest., 1997, 100, 2022) and that accumulation of macrophages and formation of atherosclerotic lesions are decreased in CCR2 gene deficient mice (see, for example, Boring, L. et al., Nature, 1998, 394, 894; Kuziel, W. A. et al., Proc. Natl. Acad. Sci. USA, 1997, 94, 12053; Kurihara, T. et al., J. Exp. Med., 1997, 186, 1757; and Boring, L. et al., J. Clin. Invest., 1997, 100, 2552). Therefore, compounds capable of inhibiting binding of chemokines such as MIP-1 α and/or MCP-1 to the receptors, i.e. chemokine receptor antagonists can be expected to be useful as a drug which inhibits the actions of the chemokines such as MIP-1 α and/or MCP-1 on target cells; however, the drug having the actions is not known. [0015] Cyclic amine derivatives such as various kinds of piperidines or piperazines have recently been reported to have chemokine receptor antagonistic activity (see, for example, WO9724325; Hesselgesser, J. et al., J. Biol. Chem., 1998, 273, 15687; Howard, O. M. Z. et al., J. Med. Chem., 1998, 41, 2184; WO9744329; WO9802151; WO9804554; WO9825605; WO9825617; WO9825604; WO9831364; WO9856771; WO9909984; WO9904794; WO9917773; WO9937617; WO9937619; WO9737651; WO9938514; WO200014086; WO200014089; EP903349; JP9-249566, JP9-25572; and JP11-711350). The compounds, however, are different from the compounds used in the present invention.

Disclosure of the Invention

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[0016] It is an object of the present invention to provide therapies for diseases wherein the binding of chemokines such as MIP-1 α and/or MCP-1 to receptors on target cells is one of the pathogenesis by using a small-molecular compound having an inhibitory activity against the binding of the chemokines such as MIP-1 α and/or MCP-1 to the receptors on the target cells.

[0017] As a result of intensive studies, the present inventors have found that cyclic amine derivatives having an arylalkyl group, pharmaceutically acceptable C_1 - C_6 alkyl-addition salts thereof or pharmaceutically acceptable acid-addition salts thereof have an inhibitory activity against the binding of chemokines such as MIP-1 α and/or MCP-1 to the target cells and that the compounds can be useful as remedies or prophylactics for diseases considered to be associated with the chemokines such as MIP-1 α and/or MCP-1. The present invention has been accomplished on the basis of the findings.

[0018] That is, the present invention is remedies or prophylactics for diseases in association with chemokines or chemokine receptors comprising compounds represented by the following formula (I), pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable C_1 - C_6 alkyl addition salts thereof as an active ingredient,

$$\begin{array}{c}
R^{1} \longrightarrow (CH_{2})_{j} - N \longrightarrow (CH_{2})_{n} \longrightarrow (CH_{2})_{n} - N - C \longrightarrow (CH_{2})_{p} \longrightarrow (CH_{2})_{q} - G - R^{6} \\
R^{2} \longrightarrow (CH_{2})_{m} \longrightarrow (CH_{2})_{m} \longrightarrow (CH_{2})_{n} \longrightarrow (CH_{2})_{p} \longrightarrow (CH_{2})_{q} - G - R^{6}
\end{array}$$
(I)

wherein

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R1 is a phenyl group, a C3-C8 cycloalkyl group or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms; the phenyl group or the aromatic heterocyclic group in the R1 may be condensed with a benzene ring or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms to form a condensed ring; the phenyl group, the $m C_3$ - $m C_8$ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R1 may be substituted with an optional number of halogen atoms, hydroxy groups, cyano groups, nitro groups, carboxy groups, carbamoyl groups, C₁-C₆ alkyl groups, C3-C8 cycloalkyl groups, C2-C6 alkenyl groups, C1-C6 alkoxy groups, C1-C6 alkylthio groups, C3-C5 alkylene groups, C_2 - C_4 alkylenoxy groups, C_1 - C_3 alkylenedioxy groups, phenyl groups, phenoxy groups, phenylthio groups, benzyl groups, benzyloxy groups, benzoylamino groups, C_2 - C_7 alkanoyl groups, C_2 - C_7 alkoxycarbonyl groups, C_2 - C_7 alkanoyloxy groups, C_2 - C_7 alkanoylamino groups, C_2 - C_7 N-alkylcarbamoyl groups, C_4 - C_9 N-cycloaikylcarbamoyl groups, C₁-C₆ alkylsulfonyl groups, C₃-C₈ (alkoxycarbonyl)methyl groups, N-phenylcarbamoyl groups, piperidinocarbonyl groups, morpholinocarbonyl groups, 1-pyrrolidinylcarbonyl groups, bivalent groups represented by the formula; -NH(C=O)O-, bivalent groups represented by the formula: -NH(C=S)O-, amino groups, mono(C1-C6 alkyl)amino groups or di(C1-C6 alkyl)amino groups; the substitutent groups of the phenyl group, the C3-C8 cycloalkyl group, the aromatic heterocyclic group or the condensed ring may further be substituted with an optional number of halogen atoms, hydroxy groups, amino groups, trifluoromethyl groups, C₁-C₆ alkyl groups or C₁-C₆ alkoxy groups,

 R^2 is a hydrogen atom, a C_1 - C_6 alkyl group, a C_2 - C_7 alkoxycarbonyl group, hydroxy group or a phenyl group; the C_1 - C_6 alkyl group or the phenyl group in the R^2 may be substituted with an optional number of halogen atoms, hydoxy groups, C_1 - C_6 alkyl groups or C_1 - C_6 alkoxy groups, with the proviso that R^2 is not hydroxy group when j is 0; j is an integer of 0 to 2;

k is an integer of 0 to 2;

m is an integer of 2 to 4;

n is 0 or 1;

 R^3 is a hydrogen atom or a C_1 - C_6 alkyl group which may be substituted with (one or two phenyl groups which may respectively be substituted with an optional number of the same or different halogen atoms, hydroxy groups, C_1 - C_6 alkyl groups or C_1 - C_6 alkoxy groups);

 R^4 and R^5 are the same or different and are each a hydrogen atom, a hydroxy group, a phenyl group or a C_1 - C_6 alkyl group; the C_1 - C_6 alkyl group in the R^4 and R^5 may be substituted with an optional number of halogen atoms, hydroxy groups, cyano groups, nitro groups, carboxy groups, carbamoyl groups, mercapto groups, guanidino groups, C_3 - C_8 cycloalkyl groups, C_1 - C_6 alkoxy groups, C_1 - C_6 alkylthio groups, (phenyl groups which may be substituted with an optional number of halogen atoms, hydroxy groups, C_1 - C_6 alkyl groups, C_1 - C_6 alkoxy groups or benzyloxy groups), phenoxy groups, benzyloxy groups, benzyloxycarbonyl groups, C_2 - C_7 alkanoyl groups, C_2 - C_7 alkanoyloxy groups, benzyloxy groups, C_2 - C_7 alkanoylamino groups, C_2 - C_7 N-alkylcarbamoyl groups, C_1 - C_6 alkylsulfonyl groups, amino groups, mono(C_1 - C_6 alkyl)amino groups, di(C_1 - C_6 alkyl)amino groups or (aromatic heterocyclic groups having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms or condensed rings formed by condensation of the aromatic heterocyclic groups having the 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as the heteroatoms with benzene rings) or both R^4 and R^5 together may form a 3- to a 6-membered cyclic hydrocarbon;

p is 0 or 1;

q is 0 or 1;

G is a group represented by -CO-, -SO₂-, -CO-O-, -NR⁷-CO-, -CO-NR⁷-, -NH-CO-NH-, -NH-CS-NH-, -NR⁷-SO₂-, -SO₂-NR⁷-, -NH-CO-O- or -O-CO-NH-,

wherein R^7 is a hydrogen atom or a C_1 – C_6 alkyl group or R^7 , together with R^5 , may form a C_2 – C_5 alkylene group; R^6 is a phenyl group, a C_3 – C_8 cycloalkyl group, a C_3 – C_6 cycloalkenyl group, a benzyl group or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms; the phenyl group, the benzyl group or the aromatic heterocyclic group in the R^6 may be condensed with a benzene ring or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms to form a condensed ring; the phenyl group, the C_3 – C_8 cycloalkyl group, the C_3 – C_6 cycloalkenyl group, the benzyl group, the aromatic heterocyclic group or the condensed ring in the above R^6 may further be substituted with an optional number of halogen atoms, hydoxy groups, mercapto groups, cyano groups, nitro groups, thiocyanato groups, carboxy groups, carbamoyl groups, trifluoromethyl groups, C_1 - C_6 alkyl groups, C_3 - C_8 cycloalkyl groups, C_4 - C_6 alkylenedioxy groups, phenyl groups, phenoxy groups, phenylamino groups, benzyl groups, benzoyl groups, phenylsulfinyl groups, C_2 - C_7 alkanoyl groups, C_2 - C_7 alkanoyl groups, C_2 - C_7 alkanoyl groups, C_1 - C_6 alkylsulfonyl groups, C_2 - C_7 alkanoyloxy groups, C_1 - C_6 alkylsulfonyl

groups, phenylcarbamoyl groups, N,N-di(C_1 - C_6 alkyl)sulfamoyl groups, amino groups, mono(C_1 - C_6 alkyl)amino groups, di(C_1 - C_6 alkyl)amino groups, benzylamino groups, C_2 - C_7 (alkoxycarbonyl)amino groups, C_1 - C_6 (alkylsulfonyl)amino groups or bis(C_1 - C_6 alkylsulfonyl)amino groups; the substitutent groups of the phenyl group, the C_3 - C_8 cycloalkyl group, the C_3 - C_8 cycloalkenyl group, the benzyl group, the aromatic heterocyclic group or the condensed ring may further be substituted with an optional number of halogen atoms, cyano groups, hydroxy groups, amino groups, trifluoromethyl groups, C_1 - C_6 alkyl groups, C_1 - C_6 alkyl groups, C_1 - C_6 alkyl)amino groups or di(C_1 - C_6 alkyl)amino groups.

[0019] The compounds represented by the above formula (I) have an inhibitory activity against the binding of chemokines such as MIP-1 α and/or MCP-1 to target cells and an inhibitory activity against physiological actions of the chemokines such as MIP-1 α and/or MCP-1 on the target cells.

Brief Description of Drawings

¹⁵ [0020]

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- Fig. 1 is a drawing illustrating effects of Compd. No. 1583 on arthritis when the compound is orally administered for 12 weeks.
- Fig. 2 is a drawing illustrating effects of the Compd. No. 1583 on synovial hyperplasia.
- Fig. 3 is a drawing illustrating effects of the Compd. No. 1583 on the chondrolysis of articular cartilages.
- Fig. 4 is a drawing illustrating effects of the Compd. No. 1583 on the osteolysis of subchondral bone.
- Fig. 5 is a drawing illustrating effects of Compd. No. 1245 on hindlimb footpads swelling when the compound is orally administered for 3 weeks.
- Fig. 6 is a drawing illustrating suppressive effects of the Compd. No. 1583 on proteinuria.
- Fig. 7 is a drawing illustrating suppressive effects of the Compd. No. 1245 on proteinuria.
- Fig. 8 is a drawing illustrating effects of the Compd. No. 1583 in animal models of chronic relapsing experimental allergic encephalomyelitis.
- Fig. 9 is a drawing illustrating effects of the Compd. No. 1245 in animal models of chronic relapsing experimental allergic encephalomyelitis.

Best Mode for Carrying Out the Invention

[0021] In the above formula (I), R¹ is a phenyl group, a C_3 - C_8 cycloalkyl group or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms; the phenyl group or the aromatic heterocyclic group in the above R¹ may be condensed with a benzene ring or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms to form a condensed ring; the phenyl group, the C_3 - C_8 cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R¹ may further be substituted with an optional number of halogen atoms, hydroxy groups, cyano groups, nitro groups, carboxy groups, carbamoyl groups, C_1 - C_6 alkyl groups, C_3 - C_8 cycloalkyl groups, C_2 - C_6 alkenyl groups, C_1 - C_6 alkoxy groups, C_1 - C_6 alkylene groups, C_2 - C_4 alkylenoxy groups, C_1 - C_3 alkylenedioxy groups, phenyl groups, phenyl groups, C_2 - C_7 alkanoyl groups, C_2 - C_7 alkoxycarbonyl groups, C_2 - C_7 alkanoyloxy groups, C_3 - C_8 (alkoxycarbonyl) methyl groups, N-phenylcarbamoyl groups, piperidinocarbonyl groups, morpholinocarbonyl groups, properidinocarbonyl groups, bivalent groups represented by the formula -NH(C=O)O-, bivalent groups represented by the formula -NH(C=S)O-, amino groups, mono(C_1 - C_6 alkyl)amino groups or di(C_1 - C_6 alkyl)amino groups.

[0022] The "C₃-C₈ cycloalkyl group" in R¹ means a cyclic alkyl group, and includes for example cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cyclohexyl group, cyclohexyl group and the like. The "C₃-C₈ cycloalkyl group" is preferably cyclopropyl group, cyclopentyl group, cyclohexyl group or the like.

[0023] The "aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms" in R¹ means an aromatic heterocyclic group, and includes for example thienyl group, furyl group, pyrrolyl group, imidazolyl group, pyrazolyl group, oxazolyl group, isoxazolyl group, thiazolyl group, isothiazolyl group, pyridyl group, pyrimidinyl group, triazinyl group, triazolyl group, oxadiazolyl (furazanyl) group, thiadiazolyl group and the like. The "aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms" is preferably thienyl group, furyl group, pyrrolyl group, isoxazolyl group, pyridyl group or the like.

[0024] The "condensed ring" in R¹ means a bicyclic aromatic heterocyclic group formed by condensing the phenyl group or the aromatic heterocyclic group with a benzene ring or the aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms in an optional position, and includes for example naphthyl

group, indolyl group, benzofuranyl group, benzothienyl group, quinolyl group, benzimidazolyl group, benzoxadiazolyl group, benzothiadiazolyl group, benzothiadiazolyl group and the like.

[0025] Among them, it is especially preferable for R1 to be a phenyl group, an isoxazolyl group or an indolyl group.

[0026] The "halogen atoms" as the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring mean a fluorine atom, a chlorine atom, a bromine atom, an iodine atom and the like, and fluorine atom, chlorine atom or bromine atom is specifically preferable.

[0027] The " C_1 - C_6 alkyl groups" as the substituents of R^1 mean C_1 - C_6 straight or branched alkyl groups, and include for example, methyl group, ethyl group, n-propyl group, n-butyl group, n-pentyl group, n-hexyl grou

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[0028] The " C_3 - C_8 cycloalkyl groups" as the substituents of R^1 are the same as defined in the " C_3 - C_8 cycloalkyl group" in the above R^1 , and specifically preferably include for example the same groups.

[0029] The "C₂-C₆ alkenyl groups" as the substituents of R¹ mean C₂-C₆ straight or branched alkenyl groups, and include for example vinyl group, allyl group, 1-propenyl group, 2-butenyl group, 3-butenyl group, 2-methyl-1-propenyl group, 4-pentenyl group, 5-hexenyl group, 4-methyl-3-pentenyl group and the like. The "C₂-C₆ alkenyl groups" are specifically preferably vinyl group and 2-methyl-1-propenyl group or the like.

[0030] The "C₁-C₆ alkoxy groups" as the substituents of R¹ mean groups composed of the above C₁-C₆ alkyl groups and oxy group, and methoxy group, ethoxy group or the like is specifically preferable.

[0031] The " C_1 - C_6 alkylthio groups" as the substituents of R^1 mean groups composed of the above C_1 - C_6 alkyl groups and thio group, and methylthio group, ethylthio group or the like is specifically preferable.

[0032] The " C_3 - C_5 alkylene groups" as the substituents of R^1 mean C_3 - C_5 bivalent alkylene groups, and include for example, trimethylene group, tetramethylene group, pentamethylene group, 1-methyltrimethylene group and the like. The " C_3 - C_5 alkylene groups" are specifically preferably trimethylene group, tetramethylene group or the like.

[0033] The "C₂-C₄ alkylenoxy groups" as the substituents of R¹ mean groups composed of C₂-C₄ bivalent alkylene groups and oxy group and include, for example, ethylenoxy group (-CH₂CH₂O-), trimethylenoxy group (-CH₂CH₂CH₂O-), 1,1-dimethylethylenoxy group (-CH₂C(CH₃)₂O-) and the like. The "C₂-C₄ alkylenoxy groups" are specifically preferably ethyleneoxy group, trimethylenoxy group or the like.

[0034] The "C₁-C₃ alkylenedioxy groups" as the substituents of R¹ mean groups composed of C₁-C₃ bivalent alkylene groups and two oxy groups and include, for example, methylenedioxy group (-OCH₂O-), ethylenedioxy group (-OCH₂CH₂O-), trimethylenedioxy (-OCH₂CH₂CH₂O-) group and propylenedioxy (-OCH₂CH(CH₃)O-) group and the like. The "C₁-C₃ alkylenedioxy groups" are specifically preferably methylenedioxy group, ethylenedioxy group or the like.

[0035] The "C₂-C₇ alkanoyl groups" as the substituents of R¹ mean C₂-C₇ straight or branched alkanoyl groups, and include for example, acetyl group, propanoyl group, butanoyl group, pentanoyl group, hexanoyl group, heptanoyl group, isobutyryl group, 3-methylbutanoyl group, 2-methylbutanoyl group, group, group, 4-methylpentanoyl group, 3,3-dimethylbutanoyl group, 5-methylhexanoyl group and the like, and acetyl group or the like is specifically preferable.

[0036] The "C₂-C₇ alkoxycarbonyl groups" as the substituents of R¹ mean groups composed of the above C₁-C₆ alkoxy groups and carbonyl group, and methoxycarbonyl group, ethoxycarbonyl group or the like is specifically preferable

[0037] The " C_2 - C_7 alkanoyloxy groups" as the substituents of R^1 mean groups composed of the above C_2 - C_7 alkanoyl groups and oxy group, and acetyloxy group or the like is specifically preferable.

[0038] The "C₂-C₇ alkanoylamino groups" as the substituents of R¹ mean groups composed of the above C₂-C₇ alkanoyl groups and amino group, and acetylamino group or the like is specifically preferable.

[0039] The " C_2 - C_7 alkylcarbamoyl groups" as the substituents of R^1 mean groups composed of the above C_1 - C_6 alkyl groups and carbamoyl group, and N-methylcarbamoyl group, N-ethylcarbamoyl group or the like is specifically preferable.

[0040] The "C₄-C₉ N-cycloalkylcarbamoyl groups" as the substituents of R¹ mean the above C₃-C₈ cycloalkyl groups and carbamoyl group, and N-cyclopentylcarbamoyl group, N-cyclohexylcarbamoyl group or the like is preferable.

[0041] The " C_1 - C_6 alkylsulfonyl groups" as the substituents of R^1 mean groups composed of the above C_1 - C_6 alkyl groups and sulfonyl group, and methylsulfonyl group or the like is specifically preferable.

[0042] The " C_3 - C_8 (alkoxycarbonyl)methyl groups" as the substituents of R^1 mean groups composed of the above C_2 - C_7 alkoxycarbonyl groups and methyl group, and (methoxycarbonyl)methyl group, (ethoxycarbonyl)methyl group or the like is specifically preferable.

[0043] The "mono(C_1 - C_6 alkyl)amino groups" as the substituents of R^1 mean amino groups substituted with the above C_1 - C_6 alkyl groups, and methylamino group, ethylamino group or the like is specifically preferable.

[0044] The "di(C₁-C₆ alkyl)amino groups" as the substituents of R¹ mean amino groups substituted with the same

or different two C_1 - C_6 alkyl groups described above, and dimethylamino group, diethylamino group, N-ethyl-N-methylamino group or the like is specifically preferable.

[0045] Among those described above, examples of the substituents of the phenyl group, the C_3 - C_8 cycloalkyl group, the aromatic heterocyclic group or the condensed ring in R¹ are specifically preferably halogen atoms, hydroxy groups, C_1 - C_6 alkyl groups, C_2 - C_6 alkenyl groups, C_1 - C_6 alkoxy groups, C_1 - C_6 alkylthio groups, C_2 - C_4 alkylenoxy groups, methylenedioxy groups, N-phenylcarbamoyl groups, amino groups, mono(C_1 - C_6 alkyl)amino groups and di(C_1 - C_6 alkyl)amino groups.

[0046] Moreover, the substituents of the phenyl group, the C_3 - C_8 cycloalkyl group, the aromatic heterocyclic group or the condensed ring in R^1 may further be substituted with an optional number of halogen atoms, hydroxy groups, amino groups, trifluoromethyl groups, C_1 - C_6 alkyl groups or C_1 - C_6 alkoxy groups. The halogen atoms, C_1 - C_6 alkyl groups and C_1 - C_6 alkoxy groups are the same as defined for the substituents of the phenyl group, the C_3 - C_8 cycloalkyl group, the aromatic heterocyclic group or the condensed ring in R^1 , and the same groups are specifically preferable. [0047] In the above formula (I), R^2 is a hydrogen atom, a C_1 - C_6 alkyl group, a C_2 - C_7 alkoxycarbonyl group, a hydroxy group or a phenyl group; and the C_1 - C_6 alkyl group or phenyl group in R^2 may be substituted with an optional number of halogen atoms, hydroxy groups, C_1 - C_6 alkyl groups or C_1 - C_6 alkoxy groups, with the proviso that R^2 is not a hydroxy group when j is 0.

[0048] The C_1 - C_6 alkyl group and C_2 - C_7 alkoxycarbonyl group in R^2 are each the same as defined for the substituents of the phenyl group, the C_3 - C_8 cycloalkyl group, the aromatic heterocyclic group or the condensed ring in R^1 , and the same examples are specifically preferable.

[0049] The halogen atoms, C₁-C₆ alkyl groups and C₁-C₆ alkoxy groups as the substituents of the C₁-C₆ alkyl group or the phenyl group in R² are the same as defined for the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R¹, and the same examples are specifically preferable

[0050] Among them, it is especially preferable for R² to be a hydrogen atom.

[0051] In the above formula (I), j is an integer of 0 to 2, and it is especially preferable for j to be 0.

[0052] In the above formula (I), k is an integer of 0 to 2; m is an integer of 2 to 4. Among them, it is especially preferable for the compounds to be 2-substituted pyrrolidines wherein k is 0 and m is 3; 3-substituted pyrrolidines when k is 1 and m is 2; 3-substituted piperidines wherein k is 1 and m is 3; 4-substituted piperidines wherein k is 2 and m is 2; or 3-substituted hexahydroazepines wherein k is 1 and m is 4.

[0053] In the above formula (I), n is 0 or 1.

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[0054] In particular, 3-amidopyrrolidines wherein k is 1; m is 2 and n is 0 and 4-(amidomethyl)piperidines wherein k is 2; m is 2 and n is 1 are especially preferable.

[0055] In the above formula (I), R^3 is a hydrogen atom or a C_1 - C_6 alkyl group which may be substituted with (one or two phenyl groups which may respectively be substituted with an optional number of the same or different halogen atoms, hydroxy groups, C_1 - C_6 alkyl groups or C_1 - C_6 alkoxy groups).

[0056] The C_1 - C_6 alkyl group in R^3 is the same as defined for the substituent group of the phenyl group, the C_3 - C_8 cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R^1 , and methyl group, ethyl group or propyl group is specifically preferable.

[0057] The halogen atoms, C_1 - C_6 alkyl groups and C_1 - C_6 alkoxy groups as the substituents of the phenyl groups as the substituents of the C_1 - C_6 alkyl group in R^3 are each the same as defined for substituents of the phenyl group, the C_3 - C_8 cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R^1 , and the same examples are specifically preferable.

[0058] Among them, it is especially preferable for R³ to be a hydrogen atom.

[0059] In the above formula (I), R^4 and R^5 are each the same or different and are each a hydrogen atom, a hydroxy group, a phenyl group or a C_1 - C_6 alkyl group; and the C_1 - C_6 alkyl group in R^4 and R^5 may be substituted with an optional number of halogen atoms, hydroxy groups, cyano groups, nitro groups, carboxy groups, carbamoyl groups, mercapto groups, guanidino groups, C_3 - C_8 cycloalkyl groups, C_1 - C_6 alkoxy groups, C_1 - C_6 alkylthio groups, (phenyl groups which may be substituted with an optional number of halogen atoms, hydroxy groups, C_1 - C_6 alkyl groups, C_1 - C_6 alkoxy groups or benzyloxy groups), phenoxy groups, benzyloxy groups, benzyloxycarbonyl groups, C_2 - C_7 alkanoyl groups, C_2 - C_7 alkanoyloxy groups, C_2 - C_7 alkyloarino groups, C_1 - C_6 alkyloarino groups, C_1 - C_6 alkyloarino groups, C_1 - C_6 alkyloarino groups or (aromatic heterocyclic groups having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms or condensed rings formed by condensation thereof with benzene rings) or both R^4 and R^5 together may form a 3- to a 6-membered cyclic hydrocarbon.

[0060] The C₁-C₆ alkyl group in R⁴ and R⁵ is the same as defined for the substituents of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R¹, and the same examples are specifically preferable.

[0061] The halogen atoms, C₁-C₆ alkoxy groups, C₁-C₆ alkylthio groups, C₂-C₇ alkanoyl groups, C₂-C₇ alkoxycar-

bonyl groups, C_2 - C_7 alkanoyloxy groups, C_2 - C_7 alkanoylamino groups, C_2 - C_7 N-alkylcarbamoyl groups, C_1 - C_6 alkyl-sulfonyl groups, mono(C_1 - C_6 alkyl)amino groups and di(C_1 - C_6 alkyl)amino groups as the substituents of the C_1 - C_6 alkyl group in R^4 and R^5 are the same as defined for the substituents of the phenyl group, the C_3 - C_8 cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R^1 , and the same examples are specifically preferable.

[0062] The C_3 - C_8 cycloalkyl groups and the aromatic heterocyclic groups having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms as the substituents of the C_1 - C_6 alkyl group in R^4 and R^5 are the same as defined for the above R^1 , and the same examples are preferable.

[0063] The halogen atoms, C_1 - C_6 alkyl groups and C_1 - C_6 alkoxy groups as the substituents of the phenyl groups as the substituents of the C_1 - C_6 alkyl group in R^4 and R^5 are the same as defined for the substituents of the phenyl group, the C_3 - C_8 cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R^1 , and the same examples are specifically preferable.

[0064] The "3- to 6-membered cyclic hydrocarbon" composed of R⁴, R⁵ and the adjacent carbon atoms are specifically preferably cyclopropane, cyclobutane, cyclopentane, cyclohexane or the like.

[0065] Among them, the hydrogen atom and C₁-C₆ alkyl group are especially preferable for R⁴ and R⁵.

[0066] In the above formula (I), p is 0 or 1; and q is 0 or 1. Both p and q are especially preferably 0.

[0067] In the above formula (I), G is a group represented by -CO- , -SO₂-,-CO-O-, -NR⁷-CO-, -CO-NR⁷-, -NH-CO-NH-, -NH-CS-NH-, -NR⁷-SO₂-, -SO₂-NR⁷-, -NH-CO-O- or -O-CO-NH-,

wherein R^7 is a hydrogen atom or a C_1 - C_6 alky group or R^7 , together with R^5 , may form a C_2 - C_5 alkylene group, wherein, -CO- is a carbonyl group, -SO₂- is a sulfonyl group and -CS- is a thiocarbonyl group. G is especially preferably the group represented by -NR⁷-CO- or -NH-CO-NH-.

[0068] The C_1 - C_6 alkyl group in R^7 is the same as defined for the substituents of the phenyl group, the C_3 - C_8 cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R^1 , and the same examples are specifically preferable.

[0069] The "C₂-C₅ alkylene group" composed of R⁵ and R⁷ means a C₂-C₅ straight or branched alkylene group, for example, methylene group, ethylene group, propylene group, trimethylene group, tetramethylene group, 1-methyltrimethylene group, pentamethylene group and the like, and ethylene group, trimethylene group, tetramethylene group or the like is specifically preferable.

[0070] Among them, it is especially preferable for R⁷ to be a hydrogen atom.

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[0071] In the above formula (I), R⁶ is a phenyl group, a C₃-C₈ cycloalkyl group, a C₃-C₆ cycloalkenyl group, a benzyl group or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms; and the phenyl group, the benzyl group or the aromatic heterocyclic group in the above R⁶ may be condensed with a benzene ring or the aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms to form a condensed ring; and the phenyl group, the C₃-C₈ cycloalkyl group, the C₃-C₆ cycloalkenyl group, the benzyl group, the aromatic heterocyclic group or the condensed ring in the above R⁶ may be substituted with an optional number of halogen atoms, hydroxy groups, mercapto groups, cyano groups, nitro groups, thiocyanato groups, carboxy groups, carbamoyl groups, trifluoromethyl groups, C₁-C₆ alkyl groups, C₃-C₈ cycloalkyl groups, C₂-C₆ alkenyl groups, C₁-C₆ alkoxyl groups, C₃-C₈ cycloalkyloxy groups, C₁-C₆ alkylthio groups, C₁-C₃ alkylenedioxy groups, phenyl groups, phenoxy groups, phenylamino groups, benzyl groups, benzoyl groups, phenylsulfinyl groups, phenylsulfinyl groups, C₂-C₇ alkanoyloxy groups, C₂-C₇ alkanoylamino groups, C₂-C₇ alkanoyloxy groups, N,N-di(C₁-C₆ alkyl)sulfamoyl groups, amino groups, mono(C₁-C₆ alkylsulfonyl)amino groups or bis(C₁-C₆ alkylsulfonyl)amino groups.

[0072] The C₃-C₈ cycloalkyl groups, aromatic heterocyclic groups having oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms, or condensed rings in R⁶ are the same as defined for the above R¹, and the same examples are specifically preferable.

[0073] The "C₃-C₈ cycloalkenyl groups" in R⁶ mean cycloalkenyl groups, for example, cyclobutenyl group, cyclohexenyl group, cyclohexenyl group, cyclohexenyl group, and 1-cyclopentenyl group, 1-cyclohexenyl group or the like is specifically preferable.

[0074] Among them, it is especially preferable for R⁶ to be a phenyl group, a furyl group and a theinyl group.

[0075] The halogen atoms, C_1 - C_6 alkyl groups, C_1 - C_6 alkenyl groups, C_1 - C_6 alkoxy groups, C_1 - C_6 alkylthio groups, C_1 - C_6 alkylenedioxy groups, C_2 - C_7 alkanoyl groups, C_2 - C_7 alkanoyloxy groups, C_2 - C_7 alkanoyloxy groups, C_2 - C_7 alkanoyloxy groups, C_2 - C_7 alkylcarbamoyl groups, C_1 - C_6 alkylsulfonyl groups, mono(C_1 - C_6 alkyl)amino groups and di(C_1 - C_6 alkyl)amino groups as the substituents of the phenyl group, the C_3 - C_8 cycloalkyl group, the benzyl group, the aromatic heterocyclic group or the condensed ring in R^6 are the same as defined for the substituents of the phenyl group, the C_3 - C_8 cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R^1 , and the same examples are specifically preferable.

[0076] The C_3 - C_8 cycloalkyl groups as the substituents of R^6 are the same as defined for the C_3 - C_8 cycloalkyl groups in the above R^1 , and the same examples are specifically preferable.

[0077] The " C_3 - C_8 cycloalkyloxy groups" as the substituents of R^6 mean groups composed of the above C_3 - C_8 cycloalkyl groups and oxy groups, and cyclopropyloxy group, cyclopentyloxy group, cyclohexyloxy group or the like is specifically preferable.

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[0078] The "N,N-di(C_1 - C_6 alkyl)sulfamoyl groups" as the substituents of R^6 mean sulfamoyl groups substituted with the same or different two C_1 - C_6 alkyl groups described above, and N,N-dimethylsulfamoyl group, N,N-diethylsulfamoyl group, N-ethyl-N-methylsulfamoyl group or the like is specifically preferable.

[0079] The "C₂-C₇ (alkoxycarbonyl)amino groups" as the substituents of R⁶ mean groups composed of the above C₂-C₇ alkoxycarbonyl groups and amino groups, and (methoxycarbonyl)amino group, (ethoxycarbonyl)amino group or the like is specifically preferable.

[0080] The " C_1 - C_6 (alkylsulfonyl)amino groups" as the substituents of R^6 mean groups composed of the above C_1 - C_6 alkylsulfonyl groups and amino groups, and (methylsulfonyl)amino group or the like is specifically preferable.

[0081] The "bis(C_1 - C_6 alkylsulfonyl)amino groups" as the substituents of R^6 mean amino groups substituted with the same or different two C_1 - C_6 alkylsulfonyl groups described above, and bis(methylsulfonyl)amino group or the like is specifically preferable.

[0082] Among them, halogen atoms, mercapto groups, nitro groups, thiocyanate groups, trifluoromethyl groups, C_1 - C_6 alkyl groups, C_1 - C_6 alkoxy groups, phenyl groups, phenylsulfonyl groups, C_2 - C_7 alkanoylamino groups, amino groups and the like are especially preferable for the substituents of the phenyl groups, the C_3 - C_8 cycloalkyl group, the C_3 - C_8 cycloalkenyl group, the benzyl group, the aromatic heterocyclic group or the condensed group in R^6 .

[0083] The substituents of the phenyl group, the C_3 - C_8 cycloalkyl group, the C_3 - C_8 cycloalkenyl group, the benzyl group, the aromatic heterocyclic group or the condensed ring in such R⁶ may further be substituted with an optional number of halogen atoms, cyano groups, hydroxy groups, amino groups, trifluormethyl groups, C_1 - C_6 alkyl groups, C_1 - C_6 alkyl groups, C_1 - C_6 alkyl)amino groups or di(C_1 - C_6 alkyl)amino groups.

[0084] The halogen atoms, C_1 - C_6 alkyl groups, C_1 - C_6 alkoxy groups, C_1 - C_6 alkylhio groups, mono(C_1 - C_6 alkyl) amino groups and di(C_1 - C_6 alkyl)amino groups as the substituents of the phenyl group, the C_3 - C_8 cycloalkyl group, the benzyl group, the aromatic heterocyclic group or the condensed ring are the same as defined for the substituents of the phenyl group, the C_3 - C_8 cycloalkyl group, the aromatic heterocyclic aromatic group or the condensed ring in the above R^1 , and the same examples are specifically preferable.

[0085] The remedially effective amount of the compounds represented by the above formula (i), pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable C_1 - C_6 alkyl- addition salts thereof together with a pharmaceutically acceptable carrier and/or a diluent can be prepared as a pharmaceutical composition and thus can be converted into medicines of the present invention capable of inhibiting the binding of chemokines to receptors on target cells, medicines having inhibitory actions on the binding of chemokines onto target cells or further remedies or prophylactics for diseases considered to be associated with chemokines or chemokine receptors. Namely, the cyclic amine derivatives represented by the above formula (i), pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable C_1 - C_6 alkyl addition salts thereof can be administered orally or parenterally such as intravenously, subcutaneously, intramuscularly, percutaneously or intrarectally.

[0086] For example, a tablet, a pill, a granule, a powder, a solution, a suspension or a capsule can be cited as the dosage form of the oral administration.

[0087] The tablet can be formed by using an vehicle, for example, lactose, starch or crystalline cellulose; a binder, for example, carboxymethylcellulose, methylcellulose or polyvinylpyrrolidone; or a disintegrator, for example, sodium alginate, sodium bicarbonate or sodium lauryl sulfate or the like according to a conventional method.

[0088] The pill, powder and granule can similarly be formed with using the above vehicle or the like according to a conventional method. The solution and suspension are produced with using glycerin esters, for example, tricaprylin or triacetin or alcohols, for example, ethanol according to a conventional method. The capsule is produced with filling a granule, powder or solution in a capsule such as gelatin.

[0089] A parenteral injection such as the form of an aqueous or a nonaqueous solution formulation is cited as the dosage form of subcutaneous, intramuscular or intravenous administration. For example, a isotonic sodium chloride solution is used as the aqueous solution. For example, propylene glycol, polyethylene glycol, olive oil or ethyl oleate is used for the nonaqueous solution. An antiseptic, a stabilizer or the like, if necessary, is added thereto. The parenteral injection is sterilized by suitably carrying out treatment such as filtration through a bacterial filter or combination of a disinfectant.

[0090] For example, an ointment or a cream is cited as the dosage form of percutaneous administration. The ointment is prepared by using oils and fats such as castor oil or olive oil or vaseline, and the cream is formed by using a fatty oil or an emulsifying agent such as diethylene glycol or sorbitan mono-fatty acid ester according to a conventional method.

[0091] A usual suppository such as a gelatin soft capsule is used for intrarectal administration.

[0092] The dose of the cyclic amine derivatives, pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable C_1 - C_6 alkyl addition salts thereof used in the present invention varies with the types of diseases, routs of administration, age and sex of patients and severity of diseases and the like, but is usually 1 to 500 mg/day for an adult.

[0093] Examples of the cyclic amine derivatives represented by the above formula (I) preferably include compounds having respective substituents shown in the following Tables 1.1 to 1.206

[0094] In Tables 1.1 to 1.206, "Table" means "Table", and "Compd. No." means "compound number". "Chirality" means the "absolute configuration", i.e. the absolute configuration of asymmetric carbon on the ring of the cyclic amine. "R" means that the asymmetric carbon atom on the ring of the cyclic amine has the absolute configuration of R, and "S" means that the asymmetric carbon atom has the absolute configuration of S. "-" means that the compound is a racemate or the compound has no asymmetric carbon atom on the cyclic amines.

Table 1.1

5	Compd.	R ¹ (CH ₂) _j -	k	m	n	chirality	·R³	$-(CH_2)_p + (CH_2)_q G - R^6$
10	1 .	C ← CH2-	1	2	0	•	н	-CH ₂ -N-C-
15	-2	CH-€ CH2-	1	2	0	-	. , H	- CH ₂ - N- C- CH ₃
	3	CH-2-	1	2	.0	-	н	-CH2-N-C-
20	. 4	CH-€	1	2	0	· <u>-</u>	, н	-CH ₂ -N-C-CF ₃
25	, 5	C├ - CH₂-	1	2	0	S	. н	-CH ₂ -N-CF ₃
30	· 6	· C⊢(1 •	2	0	· · · · · · · ·	H	- CH ₂ - N C -
35	7	CI—CH₂-	1	2	0	S	н	-CH ₂ -N-C-
40	8	C├ - CH₂-	1	. 2	0	S	н	- CH ₂ -N-C-
45	9	C├ - CH₂-	1	2	0	S	н	-CH₂-N-CI
50	10	C	. 1	2	0	S	н	- CH2- № C
55	11	C⊢√_CH₂-	1	2	0	S	н	-CH2-N-C
55					•			

Table 1.2

5	Compd. No.	R ² (CH ₂);-	k	m	n	chirality	· R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	12	CHZ-	1	2	0	S	н	-CH2-NC-OCH3
15	13 -	CH2-	1	2	0	S	н	-CH ₂ -N-C-CF ₃
	14	СН2-	1	2	0	S	н	- CH ₂ -N-C-CH ₃
20	15	CH₂-	1	2	0	S	н	-CH2-14-C-
25	16	CH2-	. 1	2	0	s	н	-CH3-HC- O D-OCH3
30	17 …	CH2−	· · · 1 · ·	2	0	S	H	O CI
35	18	CH-CH₂-	1	2	0	·S	н	- CH ₂ - N- C-
40	19	CH2-	1	2	0	S	н	-CH2-N+C-
45	20	CH2⁻	1	2	0	S	′ H	- CH ₂ -N-CF ₃ - CH ₂ -N-CF ₃ - CH ₂ -N-CF ₃
50		CH2-					н	- CH ₂ -N C- CF ₃
	22	C	1	2	0	S	н	- CH ₂ -N C - CF ₃
55								

Table 1.3

Compd. No.	R ¹ (CH ₂)	k	m	n	chirality	R ³	-(CH ₂) p G (CH ₂) q G-R ⁶
23	C├ - CH ₂ -	1	2	0	S	н	-CH2-N-C
. 24	C	1	2	0	S	Н	- CH2- N C - CH3
25	C	1	2	0	S	Н	-CH ₂ -N-C- CF ₃
26	C⊢CH₂-	1	2	0	S	н	- CH ₂ -N C-
27	CH2−	1 .	. 2	0	S	н,	-CH ₂ -N-C-NO ₂
28	C ← CH ₂ -	1	2	0	. s	'н"	- CH ₂ -N-C-NO ₂
29	C⊢CH₂-	1	2	0	R	н	-CH ₂ -N-C-CF ₃
30	C⊢√CH₂-	1	2	0	R	н	-CH ₂ -N-C
	C⊢√_CH ₂ -					н	-CH2-N-C-
32	CI—()— CH₂-	1	2	0	R	Н	- CH ₂ -N C-(
33	CH2−	1.	2	0	R	Н	- CH ₂ -N-C
	•						

Table 1.4

5	Compd. No.	R ¹ (CH ₂)j-	k	m	n	chirality	· R³	$-(CH_2)_{\overline{p}} + (CH_2)_{\overline{q}} G - R^6$
. 10	34	CH-CH2-	1	2	0	R	н	-CH2-N-C- OOCH3
	35	CI—{	1	2	0	R	н	-CH ⁵ - W C - OCH ³
15	36	CH-€CH₂-	1	2	0	R	н .	-CH2-N-C-OCH3
20	37	CH-€	1	2	0	R	н	- CH ₂ -N-C-CF ₃
25	38	CH-CH ₂ -	1	2	. 0	R	н	-CH ₂ -N-C-CH ₃
30	· ·39 ~	· CH-()-CH ₂ -· ·	-1	2	.0	R ·	Н	-CH2-HC-
35	40	CHCH ₂ -	1	2	0	R	Н	-CH2-№ C
40	41	CH-CH ₂ -	1	2	0	R	Н	- CH2- N C-CI
40	42	CH-CH ₂ -	1	2	0	R	н	- CH ₂ - N- C-
45	43	CHCH2-	1	2	0	R	н	- CH2- N C- 0
50	44	CH-{-}-CH ₂ -	1	2	0	R	н	-CH ₂ -N C -CF ₃
						·		

Table 1.5

5	Compd. No.	R ² (CH ₂)	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	45	C ├── C H₂-	1	2		R	Н	-CH ₂ -N-C-CF ₃
10	46	. C⊢-(CH₂-	1	2	0	R	н	-CH ₂ -N-C-CF ₃
15	47	C├ ─ CH₂-	1	2	0	R	н	O OCF3
20	48	CHCH ₂ -	1	2	0	R	н	-CH ₂ -N-C
25	49	C├ \ CH ₂ -	1	2	0	R R	н	- CH ₂ -N-C
30	50	CH2 ⁻	1	2	0	R	· н -	- CH2- N C- CF3
35	51	CHCH ₂ -	1	2	0	R .	H	-CH ₂ -N-C-Br
	52	C├ \ CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
40	53	C├ - CH₂-	1	2	0	R	н	-CH ₂ -N-C-CI
45								
50	55	CH_CH2-	1	2	0	R	Н	- CH ₂ -N-C-CI
			<u> </u>					

Table 1.6

Compd.	R ¹ (CH ₂)	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
56	с⊢С}-сн₂-	1	2	0	R	Н	-CH2-NC-
57	C⊢-{CH ₂ -	1	2.	0	R	Н	-CH ₂ -NC-
58	C├ - CH ₂ -	1	2	0	R .	н	-CH2-N-C-
59	CH ₂ -	1	2	0	R	н	- CH ₂ - N C - Br
60 	C⊢√ CH₂-	1	2	0	R.	н	-CH ₂ -N-C-
61	C⊢-(CH₂-	1 ·	2 .	0	R	H-	-CH ₂ -N-C
62	CHCH2-	1	2	0	R	н	-CH ₂ -N-C
63	CHCH ₂ -					H	- CH ₂ - N- C- СH ₂ CH ₃
							-CH2-N-C- H-C- CN
65	CH-2-	1	2	0	R	H	-CH ₂ -N-C-
66	CH-2-	1	2	0	R	Н	-CH ₂ -N-C-
						·	

Table 1.7

Compd. No.	R 1 (CH ₂)j-	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
67	CI—CH₂-	1	2	0	R	н	-CH ₂ -N-C
68	CH-2-	1	2	0	R	н	-CH ₂ -N-C
69	C ⊢ C H₂-	1	2	0	R	H	-CH ₂ -NC-F
70	CH-2-	1	2	0	R	н	-CH ₂ -N-C
. 71	C⊢—CH₂-	1	2	0	R	. н	-CH ₂ -N-C
72	CH-€-CH2-	1	. 2	0	R	" " H	-CH ₂ -N-C
73	CH-€	1	2	0	R	H	-CH ₂ -N-C- F₃CO
74	CH-2-	1	2	0	R	Н	-CH ₂ -N-C
75	CI—CH₂	1	2	0	R		-CH₂-N-C- F ₃ C
76	C⊢————————————————————————————————————	1	2	0	R	н	-CH ₂ -N-C
77	CH-CH₂-	1	2	0	R	н	-CH ₂ -N-C
							

Table 1.8

	*							
5	Compd. No.	R ¹ (CH ₂)	k	m	n	chirality	Ŕ³	—(CH ₂) p (CH ₂) q G-R⁶ R ⁵
10	78	C├─ \ CH ₂ -	1	2	0	R	Н	-CH2-NC
	79	CHCH ₂ -	1	2	0	R	. н	-CH ₂ -NC-CF ₃
15	80	CH_CH ₂ -	1	2	0	R		-CH ₂ -N-C
20	81	CH2-	1	2	0	R	н	-CH ₂ -N-C-CH ₃
25	82	CH-CH ₂ -	· 1	2	0		−сн ³	-CH2-N-C-CF3
30 ·	83	CH-CH2-	1	2	0	R	н	-CH ₂ -N-C-NO ₂
35	84	CH-2-	1	2	0	R	н	-CH ₂ -N-CNO ₂
40	85	CH-CH ₂ -	1	2	0		н	-(CH ₂) ₂ -N-C-
45	86	CH-CH2-	1	2	0	. -		-(CH ₂) ₂ -N-C-NO ₂
	87	CH-CH2-	1	2	0	S	н	-(CH ₂) ₂ -N-C-CF ₃
50		CI—CH₂-					н	-(CH ₂) ₂ -N-C-CF ₃ -(CH ₂) ₂ -N-C-CF ₃ F ₃ C
55								

Table 1.9

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5	Compd. No.	R ¹ (CH ₂) _j -	k	m	n	chirality	· R³	-(CH ₂) _p +5 (CH ₂) _q G-R ⁶
10	89	CH2-	1 .	2	0	S	. н	-(CH ₂) ₂ -N-C
45	90	C	1,	2	0	S	н	-(CH ₂) ₂ -N-C
15	91	CH₂-	1	2	0	S	н	-(CH₂)₂-N-C
20	92	CH-2-	1	2	0	S	н	-(CH ⁵) ⁵ - ^H - C − OC H ³
25	93	. CH2-	1	2	0	S	н .	-(CH ₂) ₂ -N-C- OCH ₃
30	- 94	CH-CH ₂	1	2	0	S	н	(CH ₂) ₂ -N-C-OCH ₃
35	95	CH-CH2-	1	2	0	S	H .	-(CH ₂) ₂ -N-C-CF ₃
40	96	CI—CH₂-	1	2	· 0	S	Н	-(CH ₂) ₂ -N-C-CH ₃
	97	CH-CH ₂ -	1	2	0	S	н	-(CH ₂) ₂ -N-C-C1
45	98	CH₂-	1	2	0	S	н	-(CH ₂) ₂ -N-C
50	99	CH-€CH3-	1	2	0	S	н	-(CH ₂) ₂ -N-C-CI

Table 1.10

Compd. No.	R ² (CH ₂) _j -	k	m	n	chirality	R³	-(CH ₂) p (CH ₂) q G-R ⁶
100	с⊢(сн₂-	1	2	0	S	н	-(CH ₂) ₂ -N-C-CN
101	CH-2-	1	2	0.	S	н	-(CH ₂) ₂ -N-C-
102	CH-CH2-	1	2	0	S	н	-(CH ₂) ₂ -N-C-
103	CH-2-	1	2	0	S	. н	-(CH ₂) ₂ -N-C- F
104	CH2−	1	2	0	S	н	-(CH ₂) ₂ -N-C-CF ₃
105 ·	CH2-	1.	2	0	·· s·	н	(CH ₂) ₂ - N- C- CF ₃
106	CH2-	1	2	0	S	н	-(CH ₂) ₂ -N-C-
	CH-2					H.	-(CH ₂) ₂ -N-C-F
108	с⊢СН₂-	1	2	0	S.	н	-(CH ₂) ₂ -N-C- H O ₂ N
109	CH2-	1	2	0	S	н	-(CH ₂) ₂ -N-C-NO ₂
110	C├ - CH ₂ -	1	2	0	S	н	-(CH ₂) ₂ -N-C

Table 1.11

5	Compd.	R ¹ (CH ₂)	k	m	n	chirality	.· R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	111	CH2-	1	2	0	R	н	-(CH ₂) ₂ -N-C-CF ₃
15	112	C - C H₂-	1	·2	0	R	н	-(CH ₂) ₂ -N-C
	113	CH-CH2-	1	2	0	R	н	-(CH ₂) ₂ -N-C-Br
20	114	CI—CH₂-	1	2	0	R	н	-(CH ₂) ₂ -N-C-
25	115	C├ ─ CH ₂ -	1	2	Ο.	R	н	-(CH ₂) ₂ -N-C-CI
30	116	C├ - CH₂- '	1 '	2	0	· R	· н·	-(CH ₂) ₂ -N-C
35	117	C	1	2	0	R		-(CH ₂) ₂ -N-C-OCH ₃
40		C├ - CH ₂ -						-(CH ₂) ₂ -N-C-OCH ₃
45	119	C├ - CH ₂ -	1	2	0	R	н	-(CH ₂) ₂ -N-C-
50	120	C ← CH ₂ -	1	2	0	R	н	-(CH ₂) ₂ -N-C-
	121	CH2-	1	2	0	R	н	-(CH ₂) ₂ -N-C-CI
55								

Table 1.12

5	Compd. No.	R ¹ (CH ₂),	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	122	CH2-	1	2	0	R	н	-(CH ₂) ₂ -N-C
15	123	CH2-	1	2	0	R	н	-(CH ₂) ₂ -N-C-CI
15	124	CH₂-	1	2	0	R	н	-(CH2)2-N-C-(CN
20	125	C ← CH ₂ -	1	2	0	R	Н	-(CH ₂) ₂ -N-C-
25	126	C├ - CH₂-	1	2	0	, R	, н	-(CH ₂) ₂ -N-C-CF ₃
30	127	CHCH ₂ -	1	2	. 0	R ·	Н	-(CH ₂) ₂ -N-CF ₃
35	128	CHCH ₂ -	1	2	0	R	н	-(CH ₂) ₂ -N-C
40	129	CH-CH2-	1	2	0	R	Н	-(CH ₂) ₂ -N-C
45	130	C├ - CH₂-	1	2	0	R	н	-(CH ₂) ₂ -N-C
45	131	CH2-	1	2	0	R	н	-(CH ₂) ₂ -N-C
50	132	C├─ ─ CH₂-	1	2	0	R	н	$-(CH_{2})_{2}-N+C$
<i>55</i>								

Table 1.13

5	Compd.	R (CH ₂),-	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	133	CI—CH₂-	1	2	0	R	н	-(CH ₂) ₂ -N-C-NO ₂
15	134	CH_CH ₂ -	1	2	0	R	н	-(CH ₂) ₂ -N-C
	135	С⊢СН2-	1	2	0	R	н	-(CH ₂) ₂ -N-C
20	136	CH2-	1	2	0	R .	н	-(CH ₂) ₂ -N-C
25	137	CH-CH2-	1	2	0	R ·	н	-(CH ₂) ₂ -N-C
30	138	CH2-	1'	2	Ö	R	Н	-(CH ₂) ₂ -N-C
35	139	C ← CH ₂ -	1	2	0	R	Н	-(CH ₂) ₂ -N-CI
40		CH2-					н	-(CH ₂) ₂ -N-C
45	141	CH2-	1	2	0	R	Н	-(CH ₂) ₂ -N-C- H H ∞
	142	CI—CH₂-	1	2	0	R	н	-(CH ₂) ₂ -N-C-CI
50	143	C├ ─ CH ₂ -	1	2	0	R	н	-(CH ₂) ₂ -N-C
55								

Table 1.14

5	Compd. No.	R1 (CH2)j-	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	144	CH2-	1	2	0	R	н	-(CH ₂) ₂ -N-C-
	145	CH-2-	1	2	0	R	н	-(CH ₂) ₂ -N-C
15	146	C ⊢ CH₂-	1	2	0	R	н	-(CH ₂) ₂ -N-C- H C- CH ₃
20	147	C⊢CH₂-	1	2	0	.R	н	-(CH ₂) ₂ - N C-СH ₂ CH ₃
25	148	CH-CH2-	1	2	0	R	. н	-(CH ₂) ₂ -N-C-CN
30	149	C⊢√ÇH₂-	1	·2 .	0	R	н	-(CH ₂) ₂ -N-C-
35	150	CH-CH2-	1	2	0	R	н	-(CH ₂) ₂ -N-C-
40	151	CH-CH2-	1	2	0	R	н	-(CH ₂) ₂ -N C
	152	CH	1	2	0	R	н	-(CH ₂) ₂ -NC
45	153	CH- C H₂-	. 1 °	2	0	R	н	-(CH ₂) ₂ -N-C-F
50	154	CH-(CH2-	1	2	0	R		-(CH ₂) ₂ -N-C- F
55			· 					

Table 1.15

5	Compd. No.	R ¹ (CH ₂)j-	k	m	n	chirality	R³	—(CH ₂) p (CH ₂) q G-R ⁶
10	155	CH-{-}-CH₂-	1	2	0	R	н	-(CH ₂) ₂ -N-С
. 15	156	CH-2-	1	2	0	R	Н	-(CH ₂) ₂ -N-C
	157	CH2-	1	2	0	R	н	-(CH ₂) ₂ -N-C
20	158	CH	1 .	2	0	R	н	-(CH ₂) ₂ -N-C- -∞- -∞- -∞- -∞- -∞- -∞- -∞- -∞- -∞-
25	159 _.	CH2-	1	2	0	R	Ĥ	-{CH ₂) ₂ -N·C- F F ₃ C .
<i>3</i> 0	160-	CHCH ₂ -	1	2	0	· R	• н	-(CH ₂) ₂ -N-C
35	161	CHCH2-	1	2	0:	R	н	-(CH ₂) ₂ -N-C
40	162	CHCH2-	1	2	0	R	H	-(CH ₂) ₂ -N-C
45	163	CH-CH ₂ -	1	2	0	R	н	-(CH2)2-N·C
	164	CH-CH ₂ -	1	2	0	R	н	-(CH ₂) ₂ -N-C
50		CH-2-					н	-(CH ₂) ₂ -N-C-CH ₃
55								

Table 1.16

5	Compd.	R ¹ (CH ₂)	k	m	n	chirality	R ³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	166	CH-2-	1	2	0	R	н	(S) O CF ₃ -CH-N-C-CF ₃
15	167	С⊢—СН₂-	1	2	0	R	н	CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3
	168	C├ - CH ₂ -	1	2	0	R	н .	CH3 -CH-N-C-CI
20	169	CH2-	1	2	0	R	н	(S) P C CI
25	170	CI—CH2-	1	2	0	R	н.	(S) -CH-N-C-CF ₃ CH ₃ F
30 .	171	CH2- "	1	2	0	R.	н.	(S) P -CHN-C-()-CI
35	172	CHZ−CH2−	1	2	0	·R	н	CH3 -CHM-C-
40	173	CH_CH2-	1		0	R	н	(S) P → NO ₂ - CH ₃ CH ₃
45	174	C-CH2-	1	2	0	R	н	(F) CF ₃ -CH-N-C-CF ₃ CH ₃
	175	CH2-	1	2	0	R	н	(A) b c st
50	176	CH_CH2-	1	2	0	R	н	CH3 CCI
55								

Table 1.17

5	Compd.	R ¹ /(CH ₂)j-	k	m	n	chirality	R³	-(CH ₂) _p (CH ₂) _q G-R ⁶
10	177	С⊢√_СН₂-	1	2	0	R	Н	(A) O CI -CH-N-C- CI I H CH3
15	178	CH-{_} CH₂-	1	2	0	R	н	(F) PCF3 -CH-N-C-CF3 CH3 F
13	179	с⊢Сту−сн₂-	1	2	0	R .	н	(A) -CHN-C- H CH3
20	180	CH_CH ₂ -	1	2	0	Ŕ	'H	(A) O -C+N-C-
25	181	CH-CH ₂ -	1	2	0	R	Н	(A) P NO2
30	182	CH-CH2-	1	2	0.	R e	- н	CH ₃ O CF ₃
35	183	CHCH ₂ -	1	2	0	R	н	Сн³ О В Сн³ С В Сн³ С В
40			1		0		н	- CH³ C- CH³ C- CH³ C- CI
	185	CHCH2-	1	2	0	R	н	CH ₃ O CI -CH N C CI CH ₃
45	186	C⊢CH₂-	1	2	Ö	R .	н	CH3 O CF3
50	187	CH-2-	1	2	O	R	н	CH3 O CI
65								

Table 1.18

5	Compd.	R ¹ (CH ₂),	k	m	n	chirality	R ³	-(CH ₂) _p = (CH ₂) _q G-R ⁶
10	188	C⊢-(н	Сн³ О Сн³ С Сн³
15	189	CH2-	1	2	0	R	н	CH³ 0 NO⁵
13	190	CH-2-	1	2		R	н .	CH-NC-CF3
20	191	CH ₂ -	1	2	0	R ,	н	CH-PC-PC-PC-PC-PC-PC-PC-PC-PC-PC-PC-PC-PC-
25	192	CH2-	1	2	0	R,	н	-CH-WCC
30	193	CH_CH ₂ -	1 ·	. 2	0 ·	- R	Н	CH N-C- CI
35	194	CHCH2-	1	2	0	R	н	CH ₂ CF ₃
40	195.	CH2-	1	2	0	R	н	(A) P -CHN-C-CI CHZ
	196	CHCH2-	1	2	0	R	н	CH ₂ C
45		C├ - CH₂-				R	н	CH ₂ S P CH ₂
50	198	CHCH2-	1	2	0	R	н	(5) P CF3 -CH-N-C-
55								

Table 1.19

5	Compd. No.	R ¹ (CH ₂),	k	m	ი	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	199	С⊢—СН₂-	1	2	0	Ŕ	н	(S) P B' C- CH N CH N
	200	C├ \ CH ₂ -	1	2	0	R	н	CH2 KC
15	201	C├ - CH ₂ -	1	· 2 _.	0	R	н	(5) + N-C- C1
20	202	CH-CH2-	1	2	0	R	Н	CH ₂ CF ₃
25	203	CH_CH ₂ -	, 1	2	0	R	"Н	(S) P -C+N-C-C-CI CH2-C)
30	204	.CHCH ₂ -	.1	2	0	R	H.	(5) P -CHN-C-
35	205	CHCH2-	1	2	0	R	н	(5) P NO 2 -CH-N-C
40	206	C├ ─ CH ₂ -	1	2	0	R	н	(3) P CH,
	207	C ← CH ₂ -	1	2	0	R	н	(OH ₂) ₂ -\$-CH ₃
45	208	C	1	2	0	R	н	(O-12)2-2-0-12
50	209	C	1	2	0	R	н	(O+3)2-2-CH3
				·				

Table 1.20

5	Compd.	H ² (CH ₂) _j	k	m	n	chirality	Ŕ³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	210	CI—(CH2-	1	2	0	R	н	(S) OF 3 -CH-N-C
	211	C├ 	1	2	0.	R	н	(O+2)2-3-CH3
15	212	C	. 1	2	0	R	. Н	(01 ₂) ₂ -9-CH ₃
20	213	C⊢(CH ₂ -	1	2	0	R	н	(O12)2-2-CH2
25	214	C⊢————————————————————————————————————	1	. 2	0		н	O -(CH ₂) ₃ -"
30	215	. C⊢() - CH ₂ -	, 1	2	0	₹	н	-(CH ₂) ₃ -C
35	216	C	1	2	0	-	н	-(CH ₂) ₃ -C
40	217	CH-CH2-	1	2	0	-	н	-(CH ₂) ₂ -C-OCH ₃
40 .	218	с⊢(1	2	0	-	н	-(CH ₂) ₂ -C-CH ₃
45	219	CHCH ₂ -	1	2	0	- ,	н	-(CH ₂) ₂ -C
50	220	CH ₂ -	1	2	0	-	н	-(CH ₂) ₂ -C-CH ₃
								_

Table 1.21

5	Compd. No.	R ¹ (CH ₂)	k	m	'n	chirality	R ³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	221	CHCH2-	1	2	0	-	н	-(CH ₂) ₂ -C-
15	222	CH-2-	1	2	0	-	н	-(CH ₂) ₂ -C-CI
,5	223	CH-CH2-	1	2	0	-	н	-(CH ₂) ₂ -C-(CH ₂) ₃ CH ₃
20	224	CH2-	1	2	0	-	н	- CH ₂ -\$СН ₃
25	225	CH-CH ₂ -	1	2	. 0	-	н	-(CH ₂) ₃ -C-N
30	. 226	CH-€	, 1	2	0	5 4.	. H , .	-(CH ₂) ₃ -C-N-OCH ₃
35	227	с⊢СН₂-	1	2 .	0		н	-(CH ₂) ₃ -C-NHC
40	228	CH-CH ₂ -	1	2	0	•	н	-(CH ₂) ₃ -C-N
	229	C├	1	2	0	-	н .	- OH ₂ -C-CH ₂ -C-N CH ₃ Q OH ₃
45	230	C├ - CH₂-	1	2	0	•	н	-CH ₂ -CH ₂ -C-N-F
50	231	CH-CH2-	1	2	0	• •	H .	-(CH ₂) ₃ -C·N-C·CH ₃
	_							

Table 1.22

5	Compd.	R ¹ (CH ₂)j-	k	m	n	chirality	R3	-(CH ₂) _p + (CH ₂) _q -G-R ⁶
10	232	CH-2-	1	2	0	-	Н	-(CH ₂) ₃ -C-N-
15	233	C	1.	2	0	-	н	-(CH ₂) ₃ -C-N-CH ₂ -
	234	C├ - CH ₂ -	1	2	0.	-	н	-(CH ₅) ₃ -C-N-CH ₃
20	235	CH2-	1	2	0	-	н	-a+2-6+c+5-c-H-c+3a
25	236	СН-СН2-	1	2	9		н	-CH ₂ -N-S-CH ₃ .
30	237	CH2-	1 .	2	.0	-	н	-CH ₂ -N-C-O-CH ₂ -
35	238	CH-€ CH ₂ -	1.	2	0	-	н .	- CH O C- N CI
40	239	CH ₂ -	1	2	0	S	н .	-CH ₂ -N-C-CF ₃
45	240	_CH₂-	1	2	0	S .	Н	-CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃
	241	CI −CH ₂ −	1	2	0	S	Н	-CH₂-N-C
50	242	CI CH ₂ -	1	2	0	S	н	-CH2-N-C-CF3
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Table 1.23

5	Compd.	R ² -(CH ₂) _j -	k	m	n	chirality	. R3	$-(CH_2)_{p} + (CH_2)_{q} G - R^6$
10	243	CI CH2-	1	2	0	S	Н	-CH ₂ -N-C-
	244	CH ₃	1	2	0	S	н	-CH ₂ -N-C-CF ₃
15	245	F_CH ₂ -	1	2	0	S	н	-CH ₂ -N-C-CF ₃
20	246	CL CH ₂ -	1	2	0	S	н	-CH ₂ -N-C-CF ₃
25	247	CH2-CH2-	1	2	0	.s	н	-CH ₂ -N-C
30	- 248	H ₃ CQ CH ₂ -	1	2	.0	, , S, ,	Н	-CH ₂ -N-C-CF ₃
35	249	F ₃ C —CH ₂ -	1	2	0	S	Н	-CH ₂ -N-C-CF ₃
40	250	H ₃ C CH ₂ -	1	2	0	S	н	-CH ₂ -N-C-CF ₃
45	251	F-CH2-	1 :	2	0	S	н	-CH ₂ -N-C-CF ₃
	252	H³CO-{CH³-	1	2	0	S	н	-сн ₂ -N-с-С _{F3}
50	253	H ₃ C-CH ₂ -	1	2	0	S	н	-CH2-N-C-CF3
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Table 1.24

5	Compd.	R ² /(CH ₂);-	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	254	NO ₂	1	2	0	S	Н	-сн ₂ -N-с-С-
	255	O ₂ N —CH ₂ —	1	2	0	S	.Н	-сн ₂ -N-С-С ₅
15	256	0 ₂ N-CH ₂ -	1	2	0	S	н	-сн ₂ -N-С-СF ₃
20	257	CF₃ CH₂-	1	2	0	S	Н	-сн ₂ -N-с-С _{Б3}
25	258	CO2CH2CH3	1	2	0	s .	н	-CH ₂ -N-C-CF ₃
30	259	CH3	1	2.	Ō	, , S ,	,.H	CF ₃
35	260	CI CI	1	2	0	s	н	-сн₂-N-С-СБ3
40	261	F ₃ C-CH ₂ -	1	2	0	S _.	н	-сн ₂ -N-с-С _Б
	262	Br CH ₂ -	1.	2	0	S	н	-сн ₂ -N-с-СF ₃
45		Br_CH ₂ -						
50	264	OH2-	1	2	0	S	н	-CH ₂ -N-C-CF ₃
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Table 1.25

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5	Compd.	R ¹ (CH ₂)-	k	m	n	chirality	R³	-(CH ₂) p 6 (CH ₂) q G-R⁶
10	265	8CH ₂ -	1	2	0	S	н	-CH2-N-C CF3
15	266	CH ₂ -	1	2	. 0	S	н	-CH ₂ -N-C-CF ₃
13	267	OCH₃ —CH₂-	1	2	0	S	. н	-CH ₂ -N-C-CF ₃
20	268	PC-C-H → OHE	1	2	0	S	н	-CH₂-N-C CF₃
25	269	H3C-\$	1	2	0	S	. н	-CH2-N-C-CF3
30	270	H₃CO₂C CH₂-	1	2	0	S	H	-CH ₂ -N-C-CF ₃
35	271	CH ₂ -	1	2	0	S	Н	-CH ₂ -N-C-CF ₃
40		но-{СН₂-					н	-CH ₂ -N-C-CF ₃
_	273	CN CH₂-	. 1	2	0	S	Н	-CH ₂ -N-C-CF ₃
45	274	NÇ CH₂-	1	2	0	S	н	-CH2-N-C-CF3
50	275	NC-{\rightarrow}-CH ₂ -	1	2	0	S	н	-CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃

Table 1.26

	Compd	R ¹ (CU)				-1-1114		$-(CH_2)_{p} + \frac{R^4}{CH_2} (CH_2)_{q} - G - R^6$
5	No.	R ¹ (CH ₂);	K	m	n	chirality	H³	-(CH ₂) _p + (CH ₂) _q G-H° R ⁵
10	276	F-CH2-	1	2	0	S	н	-CH2-N-C-C-CF3
15	277	OH₂-	1	2	0	S	н	-CH ³ -N-C-C-CL ³
,3	278 .	н₃∞₂с-{сн₂-	1	2	0	S	н	-CH ₂ -N-C-CF ₃
20	279	F₃CO-{CH₂-	1	2	. 0	s	н	-CH ₂ -N-C-CF ₃
25	280 .	F ₃ CO —CH ₂ -	1	2	0	S	н,	-CH _{2-N} -C-CF ₃
30	281	HO ₂ C-CH ₂ -	1	2	0	S	Н	-CH ₂ -N-C-CF ₃
35 ·	282	(H ₃ C) ₃ C	1	2	0	S	н	-CH ₂ -N-C
40	283	CH ₃ CH ₂ -	1	2	0	S	н	-CH2-N-C-C-CF3
45		CH-CH-					н	-CH ₂ -N-C-CF ₃
	285	(CH₂-	1	2	0	R	н	-CH ₂ -N-C-CF ₃
50	2̈86	CH ₂ -	1	2	0	R	Н	-CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃
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Table 1.27

Compd	. R ¹ (CH ₂)	k	m	n	chirality	D3	-(CH ₂) _p + (CH ₂) _q G-R ⁶
No.	R ² 21						R ⁵
287	CI CH2-	1	2	0	R	н	-CH ₂ -N-C-CF ₃
288	CH_CH ₂ -	1	2	0	R ·.	н	-CH ₂ -N-C-CF ₃
289	CI CI CI	1	2	0	Ħ.	н	-CH ₂ -N-C-CF ₃
290	CH₃ —CH₂-	1	2	0	R .	н	-сн ₂ -N-с-С-С-
291	CH ₂ -	1	2	0	R	Н	· -сн ₂ -N-с-С ₂
292	CI CH₂- '	.1	2	0	R	н	-CHZ-N-C-CF3
293	CICH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
294	H ₃ CQ CH ₂ -	1	2	0	R	Н	-CH ₂ -N-C-CF ₃
295	F ₃ C ————————————————————————————————————	1	2	0	R	н	-CH ₂ -N-C-CF ₃
296	H ₃ C —CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
297	F-(CH ₂ -	1	2	0	R	, н	-CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃

Table 1.28

Compd. No.	R ¹ (CH ₂);-	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
298	н₃со-{_}сн₂-	1	2	0	R	н	-CH2-N-C- CF3
299	H ₃ C-\CH ₂ -	·1	2	0	R	·Ħ	-CH2-N-C- CF3
300	NO ₂	1	2	0	R	н .	-CH2-N-C- CF3
301	O ₂ N	1	2	0	R.	н	-CH2-N-C-CF3
302	O ₂ N-()-CH ₂ -	1	2	0	R	н	·-CH₂-N-C CF3
303	CF ₃	1	.2	0	R	H	-CH ₂ -N-C-CF ₃
304	CO₂CH₂CH₃	1	2	0	R	н.	-CH ₂ -N-C-CF ₃
305	CH3					н	-CH ₂ -N-C-CF ₃
306	CI CH ₂ —	1	2	0	Pi .	н	-CH ₂ -N-C-CF ₃
307	F ₃ C-\(\bigcap\)CH ₂ -	1	2	0	R	н .	-CH-N-C-
308	Br −CH₂−	1	2	0	R	н	-CH ₂ -N-C-CF ₃
,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,							

Table 1.29

Compd. No.	R ¹ (CH ₂)j-	k	. w	n	chirality	H3	—(CH ₂) p (CH ₂) q G−R ⁶
309	B¢ CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
310	OH2-	1	2	0	R	н	-CH ₂ -N-C-CF ₃
311	Br—CH₂−	1	2	0	R	н	-CH2-N-C-C-CF3
312	СН,-	i1	2	0	R	н	-СH ₂ -N-С-СБ ₃
313	ОСН ₃ —СН ₂ -	. 1	2	0	R	н	-CH ₂ -N-G-CF ₃
314	4c-c-H-O-01₹	1.	2	0	R	н	-сн ₂ -N-с-С ₃
315	H ₂ C-\$	1	2	0	R	н	-CH ₂ -N-C-CF ₃
316	H ₃ CO ₂ C CH ₂ -	1	2	0	R.	H	-CH ₂ -N-C-CF ₃
						н	-CH2-N-C-CF3
318	. но-{Сн₂	. 1	2	0	R	н	-CH ₂ -N-C-CF ₃
319	CN CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃

Table 1.30

5	Compd.	R1 (CH2);-	k	m	n	chirality	R³	-(CH ₂) _p +(CH ₂) _q G-R ⁶
10	320	NC CH₂-	1	2	0	R	н	-CH ₂ -N-C-
	321	NC-CH ₂ -	1	2	0	R	Н	-CH ₂ -N-C-CF ₃
15	322	F-CH ₂ -	1	2	0	R	н	-сн _z -N-с-С _г
20	323		1	2	0	R	н	-CH2-N-C CF3
25	324	H₃∞₂C-√CH₂-	1	.2	0	R	н	-сн ₂ -N-с-СБ3
30	325	F3CO-CH2-	1	2	0	R	H	-CH ₂ -N-C-CF ₃
35	326	F ₃ CQ —CH ₂ -	1	2	0	R	н	-сн ₂ -N-с-СF ₃
40	327	HO ₂ CCH ₂ -	. 1	2	0	R	н	-сн ₂ -р-с-СF ₃
45	328	(H ₃ C) ₃ C-\(\bigc\) CH ₂ -	1	2	0	R	н	-CH2-N-C-CF3
.3	329	CH ₃ CH ₂ - CH ₃	1	2	0	R	н	-CH ₂ -N-C-
50	330	CI—CH ₂ -	0	3	1	-	. н	-CH2-H C-
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Table 1.31

Compd. No.	R ² (CH ₂);-	. k	m	n	chirality	. R³	—(CH ₂) p
331	CI-CH ₂ -	0	3	1	-	н	- CH ₂ - N- C-CH ₃
332	CH-€	0	3	1		н	- CH2- N- C
333	C├ - CH₂-	0	3	1	-	н	-CH2-N-C-
334	CH-CH2-	0	3	1	-	н	-CH2-N-C
335	C├ - CH₂-	0	3	, 1	-	н	-CH ₂ -N-C-NO ₂
·336	C(CH₂-	0	3	1	•	н	-CH2-N-C-CF3
337	CH-CH ₂ -	0	, 3	1	-	н	-CH ₂ -N-C-
338	CH-CH ₂ -	0	3	1	-	н	-CH ₂ -N-C-C-CH ₃
339	C⊢(CH₂-	0	3	1	R	н	- CH2-N-C-CF3
340	C	0	3	1	S	н	- CH ₂ - N C-
341	CH-2-	0	3	1	-	н.	-(CH ₂) ₂ -N-C-

Table 1.32

Compo	1. R ¹ (CH ₂) _j -	k	m	n	chirality	R³	-(CH ₂) ρ (CH ₂) η G-R ⁶
342	C	. 0	3	1	•	н	CH3 0 -CHN-C-
343	C├ - CH₂-	0	3	1	-	Н	CH(CH3)2
344	CH-CH2-	0	3	1	-	. H	O -CH N-C- H H CH2CH(CH3)2
345	CH-CH2-	0	3	1	-	н	-(CH ₂) ₃ -C-
346	сСН2-	0	3	1		Н	-(CH ₂) ₂ -C
347	C├ - CH₂-	0 -	3	1	<u>.</u> .	H	-(CH ₂) ₂ -CH ₃ H ₃ C
348	C	0	3	1	· <u>-</u>	н	-(CH ₂) ₂ -C-CH ₃
349	CH2-	0	3	1	-	н	-CH ₂ -S-CH ₃
350	CH2−	0	3	1	-	н	-CH ₂ -N-S-CH ₃
351	CH2-	0	3	1	-	н	-сн ₂ -м-с-о-сн ₂ -
352	CH-CH2-	0	3	11	-	н	-CHO.C.N-CI

Table 1.33

Compd. No.	R ¹ (CH ₂);-	k	m	n	chirality	· R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
353	C	1	2	1	- -	H	-CH2-N-C-
354	CH-2-	1	3	0	-	н	-CH ₂ -N-C-
355	с⊢С}-сн₂-	1	3	0	-	н	- CH2-N-C-CH3
356	. CH-{	1	3	0	-	н	-CH2-H-C-
357	CH-CH₂-	1	3	. 0	-,	អ	-CH2-N-C-
358	"CH-2-	1	3	0		H *	-CH ₂ -N-C-CF ₃
359	CH2⁻	1	3	0 -	-	H .	-(CH ₂) ₂ -N-C-
360	CH2⁻		3		~	н	-(CH ₂) ₂ -N-C-NO ₂
361	CH2⁻	1	3	0	· -	Н	-(CH ₂) ₃ -C-
362							-(CH ₂) ₃ -с
363	CH2-	1	3	0	-	H	-(CH ₂) ₃ -C-(S
						·	

Table 1.34

5	Compd.	R ¹ (CH ₂)-	k	m	n	chirality	[·] R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	364	CH-CH2-	1	3	0	-	Н	-(CH ₂) ₂ -C
	365	CH-CH2-	1	3	0	-	н	O -(CH ₂) ₂ -C- H ₃ C
15	366	CH2-	1	3	0	-	н	-(CH ₂) ₂ -C-C-C-CH ₃
20	367	CH2-	1	3	0	-	н	-(CH ₂) ₂ -C-CH ₃
25	368	C⊢—CH₂-	1	3	0		. н	-(CH ₂) ₂ -C-
30	369	CH_CH ₂ -	- 1 ··	3	0	-	н	-(CH ₂) ₂ -C-
35	370	CH-CH₂-	1	3	0		н	° -(СН ₂)₂-°С-(СН ₂)₃СН₃
40		CH-CH2-				-		-(CH ₂) ₂ -C-Q-Q-Q-Q-Q-Q-Q-Q-Q-Q-Q-Q-Q-Q-Q-Q-Q-Q-
45	372	CH-CH ₂ -	1	3	0	-	н	- CH ₂ -S-CH ₃
	373	CH-2-	1	3	0	-	н	-(CH ₂) ₃ -C·NH
50	374	CH-2-	1	3	0		н	-(CH ₂) ₃ -C·N-C
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Table 1.35

5	Compd.	R ¹ (CH ₂);	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	375	с⊢С-сн₂-	1	3	0	-	н	-(CH ₂) ₃ - C-N
	376	CH-CH ₂ -	1	3	0	•	` н	-(CH ₂) ₃ -С-N-С-ОСН ₃
15	377	CH_CH ₂ -	1	3	0	-	н	-CH ₂ -C-CH ₂ -C-N-CI
20	378	сн-Сн ₂ -	1	3	0	-	н	-CH ₂ -CH ₂ -CH ₂ -F
25	379.	CH-CH ₂ -	1 .	3	0	-	н	-(CH ₂) ₃ -C-N-C-CH ₃
30	380	CH-CH2-	1	3	0	÷	Н	-(CH ₂) ₃ -C-N-CH ₂
<i>3</i> 5	381	CHCH ₂ -	1	3	0	-	н	-CH ₂ -N-S-CH ₃
	382	CH-CH ₂ -	1	3	0	-	н	-CH ₂ -N-C-O-CH ₂ -
40	383	CH-CH2-	1	3	0	-	Ĥ	- cH O- C- H CI
45	384	CH-CH ₂ -	2	2	0	•	Н	
50	385	CH-CH ₂ -	2	2	0	-	н	-CH ₂ -N-C
					···			

Table 1.3.5

5	Compd. No.	H ¹ (CH ₂)	k	m	n	chirality	R³	-(CH ₂) p (CH ₂) q G-R ⁶
10	386	CH₂-	2	2	0	-	н	-CH ₂ -N-C-
	387	◯ -CH ₂ -	2	2	0	· -	н	-CH ₂ -N-C-
15	388	C H₂-	2	2	0	-	н	-CH ₂ -N-C-\(\sigma\)
20	389	⊘ −cH ₂ −	2	2	0	-	. н	-сн ₂ -N-с Н с С
25	390	. CH ₂ -	2	2	0	· -	. н •	-CH₂-N-C-
30	391	(-)−CH ₂ −	2	2 .	0	-	н	-CH ₂ -N-C
35	392	CH ₂ -	2	2	0	-	н	-CH2-N-C-COCF3
	393	CH₂-	2	2	0		н	-CH2-N-C- O Br
40	394	CH₂-	2	2	0	-	н	-CH ₂ -N-C-CI
45	395	CH ₂ -	. 2	2	0	-	H	-CH2-N-C
50								-CH₂-N-CF

Table 1.37

5	Compd. No.	R ² (CH ₂) _j -	k	m	n	chirality	R³	-(CH ₂) p G (CH ₂) q G-R ⁶
10	397	€ СН2-	2	2	0	-	н	-CH2-N-C
15	398	◯ −CH ₂ -	2	2	0	- 	н	-(CH ₂) ₂ -N-C-
	399	—CH₂-	2	2	0		н	-(CH ₂) ₂ -N-C-
20	400		2	2	0	-	н	-(CH ₂) ₂ -N-C-\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\
25	401	CH ₂ -	2	2	0	-	н	-(cH ₂) ₂ -N-c-√-∞ ₂ cH ₃
30	402	CH₂-	2	2	0	-	Ĥ	(CH ₂) ₂ −N-C
35	403	◯ -CH ₂ -	2	2	0	-	н	-(CH ₂) ₂ -N-C-CF ₃
40	404	CH₂-	2	2	0	-	н .	-(CH ₂) ₂ -N-C
	405	(2	2	0	-	н	-(CH ₂) ₂ -N-C-Br
45	406		2	2	0		н	-(CH ₂) ₂ -N-C-
50	407	СН₹-	2	2	0	-	н	-(CH ₂) ₂ -N-C-Br
55								

Table 1.38

5	Compd. No.	R ² (CH ₂)	k	m	n	chirality	·R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	408	—cH₂-	2	2	0	-	н	-(CH ₂) ₂ -N-C-F
15	409	CH2−	2	2	0	-	. н '	-(CH ₂) ₂ -N-C-CI
	410	CH _₹	2	2	0	-	н	(S) P -CH-N-C- CH ₂ CH(CH ₃) _{2:}
20	411	◯ -CH ₂ -	2	2	0	-	н	(5) 0 -CH-N-C
25	412	CH₂-	2	2	0	-	н	(5) P -CH-N-C- H CH ₂ CH(CH ₃) ₂ .
30	413	CH ₂ -	2.	2	0	en e	Н	(S) O -CH-N-C-C-CO ₂ CH ₃ CH ₂ CH(CH ₃) ₂
35	414	€ CH2-	2	2	0	-	н	(S) (CF ₃ -CH-N-C- H CH ₂ CH(CH ₃) ₂
40	415		2				н	(S) P CF ₃ -CH-N-C- CF ₃ CH ₂ CH(CH ₃) ₂ F
45	416	CH₂-	2	2	0	-	н	(S) OCF ₃ -CH-N-C- CH ₂ CH(CH ₃) ₂
43	417	CH2-					н	(S) P Br -CH-N-C- CH CH ₂ CH(CH ₃) ₂ .
50	418	CH ₂ -	2	2	0	- .	н	(5) -CH-N-C- CH ₂ CH(CH ₃) ₂
55			 -		 -			

Table 1.39

5	Compd.	R ² (CH ₂) _j	k	m	n	chirality	[:] R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	419.	CH₂-	2	2	0	-	н	(S) P −CH+N+C− CH2CH(CH3)2
15	420	(CH₂-	2	2	0	-	н	(5) - CH-N-C
	421	СН₂-	2	2	0	-	н	(S) - CH-N-C-CI CH₂CH(CH₃)₂
20	422	CH2-	2	2	0	-	н	(A) 0 - CH-N-C- EH2CH(CH3)2
25	423	-CH ₂ -	· 2	2	0	-	н	(A) O -CH-N-C- H H C CH ₂ CH(CH ₃) ₂
<i>30</i> ,	424	CH ₂	2	2	0	. •	Н.,	(F) P NO2 -CH-N-C-CH2CH(CH3)2
35 ·	425	CH²-	2	2	0	- •	н	(F) -CH-N-C- H CH ₂ CH(CH ₃) ₂ CH ₂ CH(CH ₃) ₂
40 .	426	CH ₂ -	2	2	0	-	н	(F) (CF ₃ -CH-N-C
45	427	€ CH2-	2	2	0	-	н	(A) (CF ₃ -CH-N-C- H CH ₂ CH(CH ₃) ₂ F
	428	CH2-	2	2	0.	- .	н	(A) -CH-N-C- -CH-N-C- -CH ₂ CH(CH ₃) ₂
50 .	429	CH₂-	2	2	0	-	н	(A) 0 - CH N C Br CH₂CH(CH₃)₂
55								

Table 1.40

	Compd. No.	R ² (CH ₂) ₁	k	m į	ก	chirality	R³	$-(CH_2)_p + (CH_2)_q G - R^6$
o	430		2	2	0	. · -	н	(A) P -CH-N-C- H H CH2CH(CH3)2
ī	431	CH₂-	2	. 2	0	-	н	(R) P -CH-N-C
	432	CH2-	2	2	0	-	н ·	(FI) P -CH-N-C F H CH₂CH(CH₃)₂
•	433		2	2	0	-	H	(A) -CH-N-C-CI -CH2CH(CH3)2
ī	434	с⊢—Сн₂-	1.	3	1	-	н	-CH²-N-C-
)	- 435	сн-СН2-	1	3 ,	. 1	.	, , H	CH ₂ -N-C-
;	436	CH2-	1	3	1		н	-CH ₂ -N-C-\(\sigma\)
)	437	CHCH ₂ -	1	3	1	-	Н	-сн ₂ -N-с- Н С- СО ₂ сн ₃
ĭ	438	CH2-	1	3	1	-	н	-CH ₂ -N-C-CF ₃
	439	C⊢————————————————————————————————————	1	. 3	, 1	-	н	-CH2-N-C-CF3
•	440	с⊢С СН₂-	1	3	1	•		-CH ₂ -N-C
							·	

Table 1.41

		1						-1
5	Compd. No.	R ² (CH ₂) _j	k	m	n	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} - G - R^6$
10	441	C	1	3	1	-	н	-CH ₂ -N-C-
15	442	CI-CH2-	1	3	1	-	н	-CH2-N-C-
	443	сн-Ссн-	1	3	1	•	н	-CH ₂ -N-C-(-Br
20	444	CH-CH2-	1	3	1	-	н .	-CH ₂ -N-C-F
25 .	445	CH_CH2-	1	З.	1	-	н	-CH2-N-C-CI
30	446	C├ - CH ₂ -	1	3	1	•	н .	-(CH ₂) ₂ -N-C-
35	447	CH2−	1	3	1	-	н	-(CH ₂) ₂ -N-C-
40	448	C├ - CH ₂ -	1	3	1	-	н	-(CH ₂) ₂ -N-C-
45	449	C├────CH ₂ -	1	3	1	-	• н	-(CH ₂) ₂ -N-C-_____\@2CH ₃
43	450	CH2-	1	3	1	-	Н	-(CH ₂) ₂ -N-C-CF ₃
50	451	CH-CH2-	1	3	1	-	н _.	-(CH ₂) ₂ -N-C-CF ₃ -(CH ₂) ₂ -N-C-CF ₃
55								'

Table 1.42

Compd. No.	R ¹ (CH ₂),	k	m	n chirality	Ŕ³	$-(CH_2)_{p}$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
452	CH2−CH2−	1	3	1 -	н	-(CH ₂) ₂ -N-C
453	CH-CH ₂ -	1	3	1 -	н	-(CH ₂) ₂ -N-C-Br
454 .	CH2-	1	3	1 -	н	-(CH ₂) ₂ -N-C-C
455	C	1	3	1 -	н	-(CH ₂) ₂ -N-C
456	CH2-	1	3	1 -	н	-(CH ₂) ₂ -N-C
457	CH-CH₂-	1.	3	1	н	-(CH ₂) ₂ -N-C-CI
458 ·	C⊢CH₂-	2	2	1 -	н	-CH ₂ -N-C-
459	CH-2-	2	2	1 -	н	- CH ₂ -N-C-CH ₃
460	CH-CH ₂ -	2	2	1 -	н	-сн ₂ -м-с- Н
461	CH-2-	2	2	1 -	н .	- CH2- N- C- CF3
462	CHZ-	2	2	1 -	Н	-CH2-N-C-

Table 1.43

Compd.	R ¹ (CH ₂)	k	m	n	chirality	R³	$-(CH_2)_{p}$ $+\frac{R^4}{R^5}$ $(CH_2)_{q}$ $-G-R^6$
463	CH2-	2	2	1	-	Н	- CH ₂ -N-C-
464	CH-CH2-	2	2	1	-	н	- CH ₂ -N-С- ОСН ₃ ОСН ₃
465	CH2−	2	2	1	, •	н	-CH₂-N-C-\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\
466	CH-2-	2	2	1		н	- CH2-N-C- NO2
467	C├ \ -CH ₂ -	2	2	1.		н	-CH ₂ -N-C
468	CH2-	. 2	2	.1		. H	··· - CH ₂ - N C - N(CH ₃) ₂
469	CH-CH₂-	2	2	1	-	н	-CH ₂ -N-C
470	C⊢CH₂-	2	2	1	-	н	-CH ₂ -N-C-CN
471	CH-(CH ₂ -	2	2	1	-	н	-CH2-N-C
472	CHCH2_	2	2	1	-	н	- CH ₂ -N-C
473	CH-CH₂-	2	2	1	-	н -	- CH2-N-C-C-CH3

Table 1.44

Compd.	R ² (CH ₂)j	k	m	n	chirality	Ŕ³	$-(CH_2)_{p}$ $+ \frac{R^4}{R^5}$ $(CH_2)_{q}$ $G-R^6$
474	с{-}сн ₂ -	2	2	1	- ,	н	-CH2-NC-CF3
475	CH2-	2	_ 2	1	-	· H	-сн ₂ - N С-С-Сн(Сн ₃) ₂
476	CH-CH ₂ -	2	2	1	-	н	- CH ₂ -N-C-\(\bigc\)-NO ₂
477	CH-2-	2	2	1	-	н	-013-H-C-(CH375
. 478	CH-CH2-	2	2	1	· ·	н	- CH ₂ -N-C-N H ₃ C
- 479 ·	C⊢(CH₂-	. 2	.5	1	- . / \	H .	- CH ₂ -N-C-O
480	CH-CH ₂ -	2	2	1		н	-CH2-N-C-O Br
481	CH-CH ₂ -	2	2	1	-	н	-CH2-NC-S
482	CH-€-CH₂-	2	2	1	-	н	- CH ₂ -N-CS
483	CH_CH ₂ -	2	. 2	1	-	H ·	-CH2-N-C-S-CH3
484	CH-2-	2	2	1	-	н	-CH ₂ -N-C-S-CH ₃

Table 1.45

Compd.	R ² (CH ₂) _j -	k	m	n	chirality	R³.	$-(CH_2)_{\overline{p}} + (CH_2)_{\overline{q}} - G - R^6$
485	C	2	2	1	-	н	- CH ₂ - N C CF ₃
486	CH2-	2	2	1	-	н	-CH ₂ -N-C-CN
487	C ⊢ CH₂-	2	2	1	•	н	-CH ₂ -N C-CI
488	C⊢CH₂-	2	2	1	-	н	-CH ₂ -N-C-\(\sigma\)
489	CH-CH2-	2	2	1	· <u>-</u>	, н	-CH ₂ -N-C
490	CH-2-	2.	2	-1	. .	н -	-CH2-N-C
491	C⊢√CH₂-	2	2	1		н	-CH ₂ -N-C-CF ₃
492	C	2	.2	1	-	н	-CH ₂ -N-C
493	C⊢ CH₂-	2	2	1	-	н	OC CF3 -CH2-NC-
494	C	2	2	1	-	н	- CH ₂ - N C- CF ₃
495	С⊢{	2	2	1	-	Н	- CH ₂ - N C- CF ₃
			·				

Table 1.46

Compd. No.	R ¹ (CH ₂)	k	m	n	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} - G - R^6$
496	CH2-	2	2	1	-	н	- CH ₂ -N-C
497	C	2	2	. 1	ż	н .	- CH ₂ - N-C
498	C+	2	2	1		н	-CH ₂ -N-C-
499	C ⊢ CH₂-	2.	2	1	-	н	- CH ₂ - N C - N(CH ₃) ₂
500	. CH-2-	2	2	1	•	н.	-сн ₂ -м-с- О О
501	CH ₂	2	2	1	. <u>-</u> .	н	-CH ₂ -N-C
502	CH2-	Ż	2	1	-	н	-CH ₂ -N-C
503	СҢСН2-	2	2	1	• .	н	-CH ₂ -N-C
504	C⊢—CH₂-	2	2	1	-	н	-CH2-H-C- OCH3
505	C⊢CH₂-	2	2	1	-	н	
506	C├ - CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
	<u> </u>						

Table 1.47

5	Compd.	R ² (CH ₂)	k	m	n	chirality	. R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	507	CI—CH₂-	2	2	1	-	Н	-CH2-N-C-
	508	CH-CH₂-	2	2	1	-	н	-CH2-N-C-S
15	509	CHCH ₂ -	2	2	1	-	н	-CH₂-N-C-S
20	510	CH-CH ₂ -	2	2	1	-	Н	-CH ₂ -N-C-O CH ₃
25	511	CI—, CH₂-	2	2	1	- .	н	CH ₂ -N-C-O C(CH ₃) ₃
30	512	CH ₂ -	2 -	2	1	-	н	- CH ² -N-C-CHCH ³
35	513	CH2-	2 _.	2	1	-	н	- CH ₂ -N-C-CH ₃
	514	CH-CH ₂ -	2	2	1	-	н	-CH ₂ -N-C-C(CH ₃) ₃
40	515	CH-2-	2	2	1	~	н	-СH ₂ -№ С-СН ₂ ОН
45	516	H ₂ N-CH ₂ -	2	2	1	-	н	-CH ₂ -N-C-CF ₃
50	517	H ₂ N CH ₂ -	2	2	. 1	-	н	-CH ₂ -N-C-CF ₃

Table 1.48

Compd.	R ² (CH ₂) _j	k	m	n	chirality	Ř³ ;	-(CH ₂) ρ 1 (CH ₂) η G-R ⁶
518	NH ₂	2	2	1	-	н	-CH ₂ -N-C-CF ₃
519	C-H-C-H2-	2	2	1	• .	н	-CH2-N-C-CF3
520	CHCH2-	2	2	1	-	-сн _з	-CH ₂ -N-C-CF ₃
521	CH2-CH2-	2	2	1	• :	(CH ₂) ₂ CH	-CH2-N-C
522	с⊷С,-сн₂-	2	. 2	1	, - 	-CH ₂ CH-	CH ₂ -N-C
523	с⊢С}-сн₂-	2	.2	1		(CH ₂) ₂ CH-	-CH₂-N-C-
524	с⊢—Сн₂-	2	2	1	· -	-CH₂CH-	-CH ₂ -N-C-
525	C├ - CH ₂ -	2	2	1	•	н	-cH₂-N-C
526	CH2−	2	2	1	•	н	-сн ₂ -ү-с-С
527	CH2-	2	2	1	-	н	-CH2-N-C-
528	CH-{}CH₂-	2	2	1		н	-CH ₂ -N-C-\S -CH ₂ -N-C-\S F ₃ C
							

Table 1.49

5	Compd.	R ¹ (CH ₂)	k	m	n	chirality	R³	-(CH ₂) p C (CH ₂)q G-R ⁶
10	529	CI-CH ₂ -	2	2	1		н	-CH ₂ -N-C-\ 0
	530	CI-CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
15	531	CI—CH ₂ -	2	2	1	-	н	-сн ₂ -ү-с-Сs
20	532	C├─{_}CH₃-	2	2	,1	-	н	-CH ₂ -N-C-CH ₃
25	533	CH-CH2-	2	2	1	-	н	-CH ₂ -N-C
30	- 534	C⊢-{CH₂-	.2	2	.1.	-	. "Н	-CH ₂ -N-C
35	535	CHCH ₂ -	2	2	1	-	H _	-CH ₂ -N-C-\S H ₃ C-C ₀
33	536	CH-CH2-	2	2	1	-	Н	-CH ₂ -N-C-N-CH ₃
40	537	CHCH2-	2	2	1	-	н	-CH ₂ -N-C-C(CH ₃) ₃
45	538	CH-2-	. 2	2	1	-		
50		CHCH2-					н	-CH ₂ -N-C- H-C -CH ₂ -N-C- F ₃ C

Table 1.50

5	Compd. No.	R ² (CH ₂)	k	m	n	chirality	R³	$-(CH_2)_{p} + \frac{R^4}{R^5} (CH_2)_{q} G - R^6$
	540	CI—CH₂-	2	2	1	-	H	-CH ₂ -N-C-N
	541	CI-CH ₂ -	2	2	1		н	-CH ₂ -N-C
15	542	C⊢—CH₂-	2	2	1	-	н	-CH2-N-C-CH2CH3
20.	543	CH-CH2-	2	. 2	1	-	н	-CH ₂ -N-C
25	544	CH2-	ż	2	1	-	н	-cH₂-N-C;-
30	. 545	CH-CH ₂ -	2	2	.1	÷ .	н	-CH ₂ -N-C-
35	546	CH-CH ₂ -	2	2	1	-	н	-CH2-N-C-CI
	547	CH2-	2	2	1	-	н	-CH ₂ -N-C- H .Cl
40	548	CH-CH ₂ -	2	2	. 1	-	н _.	-CH₂-N-C-CI
45	549	С⊢—СН₂-	2	2	1	-	Н	-CH ₂ -N-C-CI
50	550	CH-CH2-	2	2	1	-	н	-CH ₂ -N-C-O ₂ N CI

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	_		•	•	•

5	Compd.	H ₅ (CH ₅)	k	m	n 	chirality	R3	$-(CH_2)_{p}$ $+ \frac{R^4}{R^5}$ $(CH_2)_{q}$ $G-R^6$
10	551	с-С	2	2	1	•	н	-CH2-N-C-CH2-CH3
15	552	CH-(CH ₂ -	2	2	1		н	-CH ₂ -N-C-CH ₂ -CF ₃
15	553	с⊢С сн₂-	2	2	1	-	н	-CH ₂ -N-C-CH ₂ -CF ₃
20	554	C├ - ⟨}-CH ₂ -	2	2	1	-	н	-CH2-N-C-N-H
25	555	CH-2-	2	2	1		н	-CH2-N-C-N-CI
30	556	CH-2-	2	2 .	1	. 	н	-CH ₂ -N-C-N-CH ₃
35	557	C├ - CH₂-	. 2	2	1	-	н	-(CH ₂) ₂ -N-C-
	558	C	2	2	1	-	н	-CH N C-
40	559	C⊢—CH₂-	2	2	1	-	Н	
45	560	CH-€					н	-CH-N-C-CN
50	561	C⊢CH₂-	2	2	1	-	н	CH3 CH3 CH3 CH3 CH3

Table 1.52

5	Compd. No.	R ² (CH ₂)	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	562	CI—() CH₂-	2	2	1	-	н	-CH N C - C)
15	563	CI-CH ₂ -	2	2	1		н	- CH N C - CF3 - CH N C - CF3 - CH3 F3C
73	564	CH-2-	2	2	1		н	-CHNC-OCH2CH3
20	565	CHCH ₂ -	2	2	1 .	-	н	-CHNC-CF3
25	· 566	CH-CH ₂ -	2	2	. 1	-	н	O OCF3 -CHNC-CHC I H CH3
30	567	CH_CH2-	2	2	. 1	- ,	H.	-CHNC-CF3
35	568	C⊢-(CH₂-	2	2	1	-	н	CH ₃ CF ₃ -CH N C CF ₃
40	569	CH-CH2-	2	2	1	-	н	
	570	CI-CH ₂ -	2	2	1	-	н	- CHN C-F
45	571	CI—CH ₂ -	2	2	1	-	н	- CH+ V; C- CH- OH(OH-3)2
50	572	C⊢—CH₂-	2	2	1	-	н	-CHN CF3
							<u> </u>	

Table 1.53

5	Compd.	H ¹ /(CH ₂) _j -	k	m		chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10 .	573	CI—(CH ₂ -	2	, 2	1	<u>-</u>	н	-CHNC-S
15	574	CI-CH ₂ -	2	2	1	-	_ н	-CH N C S Br
15	575 .	CI-CH ₂ -	2	2.	1	-	н	-CH-W-C-(CH3)2
20	576	CH2-	2	2	1	-	н	-CHNC-OSCH3
25	577	CI—CH₂-	2	2	1		н	-c+ kc-
30	578	C⊢CH2~	2	2	1	- ,	. н	-CHNC-S
35	579	C⊢CH₂-	2	2	1	<u>-</u> ,	н	-CH ³ H
	580	CH2-	2	2	1	-	н	- CH N C- S CH3
40	581	C⊢CH₂-	2	2	1	- .	н	-CHNC-S
45	582	C ├── CH ₂ -	2	2	1	. -	н	-CH N C S
50	583	CI—CH₂-	2	2	1	•	н	

Table 1.54

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5	Compd.	R ² (CH ₂)	k	. m	n	chirality	R³	$-(CH_2)_{\overline{p}} + (CH_2)_{\overline{q}} - (CH_2)_{\overline{q}} - R^6$
10	584	C ⊢ CH ₂ -	2	2	1	-	н	-CH N C
	585	CH-2	2	2	1		н	-CH ¼ C
15	586	CH-Z-	2	2	1	-	н	- CH N C-CI
20	587	CI—CH₂-	2	2	1	-	н	-CHNC-CF3
25	588	CH2-	2	2	1	- ,	н	-CH-N-C-NH ₂
30	589	C├ - CH ₂ -	2	2	1	-	Н.	- CH ³ СH ³) ³
35	590	CI—CH₂-	2	2	1		н .	-CHNC-CH(CH ₃) ₂ CH ₃
40 ·	591	CH-CH₂-	2	2	1		Ĥ,	-CH-N-C
	592	CH2-	2	-2	1	-	н .	-СН И С- СН3 СН3
45	593	С⊢—СН₂-	2	2	1	-	н	-сн и с Сн³ Сн³
50	594	C ⊢ CH₂-	2	2	1		н	-сн и с- -сн и с- -сн и с-
k.								

Table 1.55

5 ,	Compd.	R ¹ (CH ₂) _j	k	m	n	chirality	K3	$-(CH_2)_{p}$ $+\frac{R^4}{R^5}(CH_2)_{q}G-R^6$
10	595	CI—(CH₂-	2	2	1	• ·	н	- CH-N C- CH3
	596	C ⊢ CH₂-	.2	2	1	•	н	-сн к с-Сн3 Сн3
15	597	C⊢-(CH₂-	2	2	1	 •	н	- CH N C - C- CH3
20	598	CH2−	2	. 2	1	<u>:</u>	н	-CHNC-0
25	599	C⊢-{CH₂-	2	2	1	-·	. н	-CH M CH3
30	60 <u>.</u> 0	CH-CH2-	2	2	1		н .	-CHNC-OBr
35	601	CH-CH ₂ -	2	2	1	-	н	-CHMC-OCH3
40	· 602	CH-{	2	2	i	-	Н	-CH-N-C-\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\
40	603	CH-2-	2	2	1	-	н	- CH-N-C
45	604	CH-CH2-	2	2	1		н	-c+++c-\
50	605	CH-{-}-CH2-	2	2	1	-	н	-CHN-C-

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Table 1.56

5	Compd.	R ² (CH ₂)	k	m	n	chirality	'R³	-(CH ₂) p G (CH ₂) q G-R ⁶
10	606	CI-CH ₂ -	2	2	1	-	н	-CH-N-C-\S
70	607	CI-CH2-	2	2	1	-	н	-CHNC-S
15	608	CI-CH ₂ -	2	2	1	-	н	-CH-N-CCH3 -CH3 H3C
20	609	C├ - CH ₂ -	2	2	1	-	н	-CH-N-CO CH3 H3C
<i>25</i>	610 .	CI—CH ₂ -	2	2	1	-	н.	-CHNC-S CH3 O-CCH3
30	611	CH-CH ₂ -	2·	2	1		н .	-CHNC-C(CH ₃) ₃ CH ₃ H ₃ C
<i>35</i>	612	 CH-CH ₂ -	2	2	1	-	н	CH NC CO
	613	CH-CH2-	2	2	1	-	н	-CHNC-CH3 CH3 F3C
40	614	С⊢СН₂-	2	2	1	-	н	-CHNC-CH ₃ -CH ₃ -CH ₃ -CH ₃ -CH ₃
45	615	С⊢—СН₂-	2	2	1	-	н	- CH-N-C
50	616	С⊢СН₂-	2	2	1	-	н	-CHNC-CH3 -CH3 F3C CH3 -CHNC-NCH3 -CHNC-NCH3 -CHNC-NCH3 -CHNC-NCH3 -CHNC-NCH3
								-

Table 1.57

5	Compd.	R ² (CH ₂)	k	m	n	chirality	Ŕ3	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	617	CI—()—CH₂-	2	2	1	-	н	-CH-N-C-CF3
	618	с⊢СH ₂ -	2	2	1	-	н	-C++ N C - CH(CH3)2
15	619	CH_CH ₂ -	2	2	1	-	н	- CH N C CN CH(CH3)2
20	620	CH-CH ₂ -	2	2	1	<u>.</u> ·	н	- CH-N-C
25	621	CH	2	2	1 .	- -	н	. −CHNC− H CH(CH3)2
30	622	CH-CH ₂ -	2	2	1	•	н	- CH N C (CH ₃) ₂ - CH(CH ₃) ₂ - CH(CH ₃) ₂
35	623	C├ - CH₂-	2	2	1	-	н	- CH N- C- O OCH3
40	624	C⊢(CH₂-	2	2	1		н	-CHNC- HH CH(CH ₃) ₂
	625	CH-CH ₂ -	2	2	1		н	- CH-N-C- - CH-N-C- - H CH(CH ₃) ₂
45	626	СН ₂ -	2	2	1		н	-CHN-C-CF3
50	627	C├ ─ ☐ CH ₂ -	2	2	1	-	н	OCH ₂ CH ₃ - CH N C C
			·					

Table 1.58

5	Compd.	R ² (CH ₂)	k	m	n	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} - (C$
10	628	С⊢-{СН₂-	2	2	1	-	н	O CO2CH3 -CH N C
	629 .	C⊢√CH₂-	2	2 .	1,	-	н	-CH N C-CF3 CH(CH3)2
15	630	CH-{	2	2	1	-	н	O OCF3 -CHNC
20	631	с⊢(СН₂-	2	2	1	-	н	-CHN-C- CH(CH ₃) ₂ CF ₃
25	632	⁻ сн-{	2	2	1	-	н	CH N C - CH CH(CH ₃) ₂ CF ₃
30	633	CH ₂ −	2	2	, 1	-	н	CF ₃ -CHNC-CF ₃ -CH(CH ₃) ₂ F
35	634	CH-CH ₂ -	2	2	1	-	н	CF ₃ -CH N C F I H CH(CH ₃) ₂
. 40	635	CH-€ CH₂-	2	2	1	-	н	CH(CH ₃) ₂ -CH-N-C
	636	C├ - ⟨}-CH ₂ -	2	2	1	•	H	- CH N C - CH3
45	637	CHCH2-	2	2	1	-	н	- CH- N C- CF ₃ - CH(CH ₃) ₂
50	638	C├ - CH₂-	2	2	1	-	Ĥ	-CH N C-
			,					

Table 1.59

5	Compd.	R ² (CH ₂)	k	m	n	chirality	Ŕ³	-(CH ₂) p 1 (CH ₂) q G-R ⁶
10	639	CHCH ₂ -	2	2	1	-	н	- CH N C - N(CH ₃) ₂ - CH(CH ₃) ₂
	640	CI—(CH ₂ -	.2	2	1	-	Н	CH(CH ³) ⁵ -CH h C O O
15	641	CI—CH₂-	2	2	1	-	н	- СН N С- Н Н СН(СН ₃) ₂
20	642	CH-CH2-	2	2	1	-	н	- CH V C-
25	643	сСн2-	2	2	1	-	Н .	- CH N C CF ₃ - CH(CH ₃) ₂
30	644	с⊢(СН₂-	2	2	1		, н .	- CH-N-C
35	645	CH-CH ₂ -	2	2	1		Н	-CHNC-NH2
	646	C├ - CH₂-	2	2	1	-	н	- СН- М-С- СН(СН3)2 СН(СН3)2
40	647	CH-CH ₂ -	2	2	1	-	н	- СН N С С СН3 СН(СН3)2
45	648	C⊢-{}-CH₂-	2	2	1	•	н	O - CH N C - CH(CH ₃) ₂ CH(CH ₃) ₂
50	649	CH-CH₂-	. 2	2	1	•	Н	- CH N C ОСН(СН3)2 СН(СН3)2
							·	

Table 1.60

5	Compd.	R ¹ (CH ₂)j-	k	m	n	chirality	R³	$-(CH_2)_{\overline{p}} + \frac{R^4}{R^5} (CH_2)_{\overline{q}} - G - R^6$
10	650	CI—(CH₂-	2	2	1	-	н	-CH-N-C
15	651	CH-CH2-	2	2	1	- ·	н	CH(O43)2
	652	CI—CH ₂ -	2	2	. 1	-	н	-CH-N-C-NO ₂ -CH(CH ₃) ₂
20	653	C├ \ CH ₂ -	2	2	1	-	н	OH(CH ³) ⁵ −CH-M-C-(CH ³) ⁴ CH ³
25	654	CH2-	. 2	2	1	· -	н	- CH- N- C CH ₃ - CH (CH ₃) ₂
30	655	с⊢(Сн₂-	· 2	2.	· 1	·· -	н	OH-N-C- CH(CH ₃) ₂
35	656	CH-€	2	2	1	-	Н	-CH-N-C-CP CH(CH ₃) ₂
40	657	CH-{-}CH₂-	2	2	1	-	н	-CH-N-C-S H CH(CH ₃) ₂
45	658	С⊢-{СH ₂	2	2	1	٤	н.	- CH-N-C-NH CH(CH3)2
45	659	с⊢ СН₂-	2	2	1	-	н	-CH-N-C- S H NO ₂
50	660	CI—(CH₂-	2	2	1	-	н	-CH-N-CN CH(CH ₃) ₂
55								

Table 1.61

5	Compd.	R ² (CH ₂)j-	k	m	n	chirality	[:] R³	-(CH ₂) p 5 (CH ₂) q G-R ⁶
10	661	CH-CH2-	2	2	1	• ·	н	-CH-N-CS H CH(CH ₃) ₂ OCH ₃
	662	СН-СН2-	2	2	1	•	н	-CHNC-CH3
15	663	CH-CH ₂ -	2	2	1	-	н	-CHN-C- CH(CH ₃) ₂
20	664	CH-2-	2	2	1	-	' н	-CH-N-C- 0: H NO ₂
25	665	C	2	. 2	1	-	н	CH(CH3)2 -CH-N-C-(S) -CH-S
30	666	CCH2-	2	2	1	-	н	-CH(CH ₃) ₂ CH ₃ CH ₃
35	667	СН ₂ -	2	2	1	-	. Н	-CH-M-C-CH-3 CH (CH3)2
40	668	CH-CH ₂ -	2	2	1	-	н	-CH-N-C
	669	CH-CH ₂ -	2	2	1	-	н	-CH'M-C- CH(CH3)2 CH3
45	67 [°] 0	CH-CH ₂ -CH ₂ -	2	2	1	-	н	-CH-N-C
50	671	CH-{	· 2	2	1	•	н	-CH-M-C-ONO ⁵
55				·				

Table 1.62

5	Compd.	R (CH ₂)	k	m	n	chirality	Ŕ³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	672	с⊢(Сн₂-	2	2	1	-	н	CH(CH²)⁵ H -CH-V-C- 0
15	673	CH2-	2	2	1	-	н	-CH-M-C-S C(CH3)2
	674	CH-CH2-	2	2	1	-	н	-ç++, c-(s) -c+(c+3)2
20	675	CH2-	2	2	1	· <u>-</u>	н	-CH-N-C- S CH ₃
25	676	C├ - CH₂-	2	2	. 1	-	н	-CH-N-C-N-CH(CH ₃) ₂ H
30	677 [.]	CH-€-	2	2	1	<u>-</u> .	н.	-CH-N-C-N-C-CH(CH ₃) ₂ CH ₃
35	678	CH_CH ₂ -	2	2	1	- -	·н	-CH-N-C
40	679	_CHCH2-	2	2	1	-	н	-CH-N-C-(S) CH(CH ₃) ₂
45	680	C├ - CH ₂ -	2	2	1	-	н	-CHN-C- Br
50		CH-(н	-CH-N-C-CH ₃ CH(CH ₃) ₂ CH ₃
50	682	CH-CH₂-	2	2	1	-	н	-CH-N-C
55			·			·		

Table 1.63

5	Compd. No.	R ¹ (CH ₂)	k	m	n	chirality	Ř³.	$-(CH_2)_{\overline{P}_5}^{\overline{P}_4}(CH_2)_{\overline{q}}G^-R^6$
10	683	с⊢(сн₂-	2	2	1	-	н	-CHN-C- S SCH3
15	684	CH-€	2	2	1	-	н	-CH-N-C- S P CH(CH ₃) ₂ S-CH(CH ₃) ₂
	685	CH2−	2	2	1	-	н	-CH-NC-() P CH(CH ₃) ₂ SCH ₃
20	686	C├ -	2	2	1	-	н	O -CHN-C- H CH ₂ CH(CH ₃) ₂
25	687	CI—CH₂-	2	2	1		н	-CH N-C-
30	688	CH-()-CH ₂ -	·2	2	1 -	- .	· H-	-c+ n-c CF3
35	689	C├	2	2	1	-	н	-ch v c-
40	690	CH-(2	2	1	-	н	-CH N-C-
45	691	C├ - CH₂-	2	2	1	-	н	-CH N C- (NCH3)2
	692	CH-CH2-	2	2	1	•	н	-CH W.C.—OCH3
50	693	C├ - \CH ₂ -					н	-CHNC
55			···-	 				

Table 1.64

5	Compd. No.	R ¹ (CH ₂);	k	m	n	chirality	Ή³	$-(CH_2)_{p} + (CH_2)_{q} G - R^6$
10 .	694	CI—CH₂-	2	2	1		н.	-CH M C OCH3CH3
15	695	CI-CH ₂ -	2	2	1		н	-CH N-C- 0 2CH3
-	696	CH-CH ₂ -	2	2	1	<u>-</u>	н	-CHNC-COCF3
20	697	CH-CH ₂ -	2	2	1	-	Н	-CH-N-C
25	698	CH-CH2-	2	2	1	٠.	н	-CH N-C- N(CH3)2
30	·· 699	с⊢Сн₂-	, 2	2	1	٠	. Н	-CH N-C
35	700	CH-€CH2-	2	2	1	•	Н	-CHN-C
40	701	C⊢-{	2	2	1	-	н	-CH N-C
45	702	CH-€	2	2	1	-	н	-CHN-C-CF3
		CH-2-						0
50								-CHN-C- NO2
55								

Table 1.65

5	Compd. No.	R ² (CH ₂);	k	m	n	chirality	R³	$-(CH_2)_{\overline{p}} + (CH_2)_{\overline{q}} G - R^5$
10	705	CI—€ CH2-	2	2	1	-	н -	-CH-N-CS
15	706	С⊢—СН₂-	2	2	1	-	н	-CHYC-STCH3
·	707	CHCH2-	2	2	1	•	н	-c+n-c
20	708	CI— CH₂-	2	2	1	-	н	-CHNC-SBr
25	.709	CH-√CH2-	2	2	1	- · ·	. н	-CHNC-STSCH3
30	-710	CH-CH2-	2	2	1		н	-CHN-C-S
<i>35</i>	711	CH-CH ₂ -	2	2	1	-	н	-CHN-C-CH3
40	712	CHCH2-			1	-	н	-chyc-st
45	713	CH-CH ₂ -	2	2	1	-	н	-CHM-C-M-C-M-C-M-C-M-C-M-C-M-C-M-C-M-C-M
50		CH2-						-CHNC-N
30	715	CH2⁻	2	2	1	-	н	-c+n-c-5
55	<u> </u>			•				

Table 1.66

5	Compd.	R ² (CH ₂)	k	m	n	chirality	R³	$-(CH_2)_{p}$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
10	716	C├ - CH ₂ -	2	2	1	-	Н	-CHMC-NH
	717	CI-CH ₂ -	2	2	1	•	H.	-CHN-C-CT NO2
15	718	C├ - CH ₂ -	2	2	1	•	н	-CH-N-C-\SH
20	719	CHCH_2-	2	2	1	-	н	-c+n-c-
25	720.	CH-€-	2	2	1	-	H	-CHNC- Br
30	721	CHCH2-	2	2	1	-	н	-CHN-C-N
35	722	CHCH2-	2	2	1	-	н	-снис-{>-сн²он
	723	CH√CH₂-	2	2	1	-	н	-CHN-C-NH2
40	724	CH-CH ₂ -	2	2	1	<u>-</u>	н	-CH-N-C-(CH3)3
45	725	CH2-	2	2	1	-	н	-c+1/-c
50		CH-CH₂-						-снис-сн ₃

Table 1.67

5	Compd. No.	R (CH ₂)	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	727	CI-CH2-	2	2	1	-	н	-CHN-C-C1
	728	CH-CH2-	2	2	1	-	н	-CH-N-C
15	729	CH2-	2	2	1	-	н	-CH-N-C
20	730	CH2-	2	2	1	-	н.	-CHN-C
25	731	C├	2	2	1	-	н,	-chyc Cocho
30	732	CH⊋-	2	2	1	-	· н	-CH-N-C
35	733	С 	2	2	1		н	-CH-N-C- HO CH(CH ₃) ₂
40	734	C├- \ CH ₂ -	2	2	1	-	H	-CH-N-C
	735	CH-€	2	2	1	-	н	-CHNC-C-3
45	736	CHCH ₂ -	2	2	1	-	н	-CHNC
50	737	CH-€ CH ₂ -	2	2	1	-	н	-CH-N-C
55								

Table 1.68

Compd. No.	R ¹ (CH ₂);	k	m	n ——	chirality	Ŕ³	-(CH ₂) _p + (CH ₂) _q -G-R ⁶
738	CH2−	2	2	1	-	н	-CHNC-CO
739	CH2−	2	2	1	-	н	-CH-N-CNH
740	CH-2-	2	2	1	-	н	-CH-N-C
741	CH-2-	2	2	1	-	Ħ	-CHNC-SNO2
742	CH-Z-	2	2	1	•	н	-CHN-C-S
743	C⊢√_CH₂-	2	2	1	and the second	. н	-снис-Со
744	CH ₂ −	2	2	1	. .	H *	-c+n-c-CH3
745	CH2-	2	2	1		н	-CHN-C-(CH3)3
	CH₂-						
747	CH2−	2	2	1	-	н	-CH-N-C
748	с⊢{_}сн₂-	2	2	1	-	н	-chyc-Cs
	<u> </u>						

Table 1.69

5	Compd.	R ¹ (CH ₂);	k	m	ח	chirality	ÌR³	$-(CH_2)_{\overline{P}} + (CH_2)_{\overline{q}} - G - R^6$
10 .	749	CH-CH ₂ -					н	-cHNC-CNO
45	750	CH-2-	2	2	1	- ^	н	-CH-N-C
15	751	CH2-	2	2	1	-	н	-CH-N-C-CH ₃ -CH ₂ OH
20	752	CH-CH2-	2	2	1	-	H	CF ₃ -CH-N-C-CF ₃ CH ₂ OH CF ₃
25	75 3	CH-CH ₂ -	2	2	1	-	н	-CH-N-C
30	754	CH-2-	2	2	·· 1		н .	CH-N-C- CH2OH
35	755	CF—€ CH2-	. 2	2	1	-	н	-CH-N-C- CH³OH
40	75 <u>6</u>	C├ - CH ₂ -	2	2	1	-	н	-CH-N-C
45	757	CHCH2-	2	2	1	-	н	OCH₂CH₃ -CH-N-C CH₂OH
	758	CHCH2-					н	CO₂CH ₃ −CH-N-C− CH₂OH
50	759	CH-2-	2	2	. 1	-	н	-CH-N-C
55							·	

Table 1.70

								R ⁴
5	Compd. No.	R ¹ (CH ₂)j-	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	760	CI—(2	2	1	-	н `	-CH-N-C-CF3 -CH ₂ OH F
15	761	C ⊢ CH₂-	2	2	1	-	អ	O CF3 -CH-N-C-CF H CH₂OH
	762	CH2-	2	2	1	-	н	-CH-N-C
20	763	с⊷СН₂-	2	2	1		н .	-CH-V-C- CH ² OH
25	764	CH2	. 2	2	1	 -	н	CH ₃ P -C-N-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-
30	765	- CH2-	. 2	2	1	-	н	CH3 O CH3
35	766	CH2-	2	2	1	-	н	CH3 0 CF3
40	767	CH2−	2	2	1	-	н	CH3 P CH3 -CH3 P CH3
_	768	СI—СН ₂ -	2	2	1	-	н	CH ₃ P. Br
45	769	,					Н	СН3 Р ОСF3 СН3
50	770	CH2-CH2-	2	2	1	-	н	-CH3 P-CF3

Table 1.71

							وموادات والمتال المتال
Compd.	R ² (CH ₂)	k	m	n	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} G - R^6$
771	CI-CH2-	2	2	1	-	н	CH ₃ P CF ₃
772	CI—CH₂-	2	2	1.	· ·	н	CH3 O CF3
773	C ← CH₂-	2	2	1	-	н	CH ₃ O C(CH ₃) ₃
774	CH-2-	2	2	1	-	н	-C-N-C- CH ₃ O SCH ₃
775	CI—CH₂-	2.	2	1	-	н	CH ₃ O CH ₃ . -C-N-C-C CH ₃ C(CH ₃) ₃
·· 776	CH-€-CH2-	2	2	1		н .	сн ₃
777	C├ - CH₂-	2	2	1	-	н	CH ₃ P CF ₃ CH ₃ CH ₃
778	CH- (CH₂-	2	2	1	-	н	CH3 0 NO2
779	CH-2-	2	2	1	-	H	CH3 Q CI
780	CH2-	2	2	1	-	н	NO-
781	CH-CH ₂ -	2	2	1	-	н	CH3 P

Table 1.72

								
5	Compd. No.	R ¹ (CH ₂)j-	k	m	n	chirality	R³	$-(CH_2)_{\overline{p}} + (CH_2)_{\overline{q}} G - R^6$
10	782	CH-CH ₂ -	2	2	1	-	Н	CH3 O OCH3
15	783	C-CH ₂ -	2	2	1	- .	н	-CH3 OCH2CH3 -CH3 CH3
	784	CI—(CH₂-	2	2	1	-	н	CF ₃ P -C-N-C-CH ₂ CF ₃
20	785	CHCH2-	2	2	1	-	н	CH ₃ P OCH ₃
25	786	C⊢√CH2-	2	2.	1	<i>;</i> -	н	-C-N-C- H ₂ C-CH ₂
30	787	C├ - CH ₂ -	2	2	1	· - .	' н	-C-N-C-CH ₃ H ₂ C-CH ₂
35	788	CI—CH ₂ -	2	2	1	-	н .	-C-N-C-CF3
40	789	CH-CH ₂ -				-	н	H ₂ C-O+ ₂
45	790	CH-CH ₂ -	2	2	1	• .	н	-C-N-C-SI
	791	CH-CH2-	2	2	1	-	н	H ₂ C-CH ₂
50	792	CH-CH2-	2	2	1	-	н	H ₂ C CH ₂ NO ₂ NO ₂ H ₂ C CH ₂ OCF ₃ H ₂ C CH ₂
55								

Table 1.73

5	Compd.	R ² (CH ₂)	k	m	n	chirality	·R³	-(CH ₂) - G (CH ₂) - G-R⁶
10	793	CI-CH ₂ -	2	2	1	<u>-</u>	н .	P CF ₃ -C-N-C-F H ₂ C-CH ₂
	794	C ├── CH₂-	2	2	1	-	н	H ₂ C—CH ₂ F
15	795	CH-CH2-	2	2	1	-	н	-C-N-C-CF ₃
20	796 [.]	CH2-	2	2	1	-	Н	H ₂ C-CH ₂
25	797	CH ₂ -	2	2	1.	-	н	O CH ₃ -C-N-C-CH ₂ C(CH ₃) ₃
30	798	CH-2-	-2	2	1	u=	н	Ho-CH3 -C-17 -C-17 -C-17 -C-17
35 ,	799	CH-2-	2	2	1	-	.н	H ₂ C—CH ₂ CF ₃ CH ₃ CH ₃
40	800	CH-2-			1		н	NO ₂ N-C-CI H ₂ C-CH ₂
45	801	CH-CH ₂ -	2	2	1	-	н	H ₂ C—CH ₂
	802	CH-CH ₂ -	2	2	1	-	н	H ₂ C—CH ₂
50	803	CH-CH₂-	2	2	1	-	н	-C-H ₂ -C-CH ₂ -C-C
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Table 1.74

5	Compd. No.	R ¹ (CH ₂)	k	m	n	chirality	R³	$-(CH_2)_{p}$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
10	804	C├─────────────────────────────	2	2	1	•	н	-C-N-C-CH ₂ -CF ₃
15	805	C⊢—CH₂-	2	2	1	-	н	H ₂ C—CH ₂ OCH ₃
	806	CH-2-	2	2	1	-	н	H ₂ C CH ₂
20	807 .	C⊢-{CH ₂ -	2	2	1	-	н	(CH ³) ² C-WH ³
25	808	C⊢-{CH ₂ -	2	2	1		н	- CH- N-C- CH3 (CH2)2-C-NH2
30	809	с⊢—СН₂-	ź	2	1''	: :	н.	(CH2)2 C-NH2
35	810	C⊢—CH₂-	2	2	1	-	н	-CH-NG-CH-3
40	811	С⊢—СН₂-	2	2	1	•	н	-CH-N-C-N-C-NO ₂
45	812	CH2-	2	2	1	•	н	-CH-N-C- H S SCH ₃ (CH ₂) ₂ -C-NH ₂
	813	CH2-	2	2	1	-	н	-CH-H-C
50	814	CH2−	2	2	1		н	-CH-N-C-NH2 -CH-N-C-NH2 -CH-N-C-NH2 -CH-N-C-NH2 -CH-N-C-NH2 -CH-N-C-NH2 -CH-N-C-NH2 -CH-N-C-NH2 -CH-N-C-NH2
55					· . • · ·			

Table 1.75

5	Compd.	R ² (CH ₂)j-	k	m	'n	chirality	R³	$-(CH_2)_{\overline{p}} + (CH_2)_{\overline{q}} G - R^6$
10	81,5	Ci—(2	2	1	•	н	- CH-N-C
15	816	с⊢(сн₂-	2	2	1	-	н	-CH-N-C
,,	817	C├ - CH₂-	2	2	1	-	٠н	-CH-N-C-NH2
20	818	CH-€	2	2	1	- '	н	- CH- N-C- Br
25	. 819	C⊢—CH₂-	2	2	1		н	-CH-N-C
30	820	C⊢————————————————————————————————————	2 ·	2	1	-	• н	-CH-N-C-NH ₂
35	821	C⊢-(CH₂-	2	2	1	-	н	-CH-N-C- CH2OCH3
40	822	CH-€ CH₂-	2	2	1	-	. н	P S SCH ₃ -CH-N-C-() SCH ₃ CH ₂ OCH ₃
	823	C⊢————————————————————————————————————	2	2	1	-	н	-CH-N-C- CH ⁵ OCH ³
45	824	CH-2-	2	2	1	-	н	CH-N-C- C(CH ₃) ₃
50	825	CH-2 ⁻	2	2	1	-	Н	-CH-N-C-Q

Table 1.76

5	Compd.	R (CH ₂)j-	k	m	n	chirality	R³	$-(CH_2)_{p}$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
10	826	с⊢{_}-сн₂-	2	2	1	-	н	-CH-N-C-CH3
15	827	CH-€CH2-	2	2	1	• · ·	н	CH ⁵ OCH ³
	828	C⊢—CH₂-	2	2	1	-	н .	OCF ₃ -CH-N-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-
20	829	CI—CH₂-	2	2		-	н	CH-N-C-CF ₃ CH ₂ OCH ₃ F
25	830	CH-CH2-	2	2	1	-	. н	-CH-N-C
30	831	CH2-	2	2	1	-	н	-CH-N-C- CH2OCH3
35 .	832 .	CH-CH ₂ -	, 2	2	1	-	н	CH-N-C-CI CH₂OCH3
40	833	CH_CH ₂ -	2	2	1	-	н .	-CH-N-C-NO ₂ -CH ₂ OCH ₃
	834	CH-2-	2	2	1	-	н	-CH-N-C- H CH ₂ OCH ₃
45	835	CH-CH2-	2	2	1	·	н	-ch-h-c-()
50	836	CH-CH ₂ -	2	2	1	-	Н	-CH-N-C-CH3 CH3OCH3
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Table 1.77

5	Compd. No.	R ¹ (CH ₂) _j -	k	m	ŋ	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} G - R^6$
10	837	CH-CH2-	2	2	1	-	н	-CH-N-C- CH2OCH3
15	838	C I— CH₂-	2	2	1		н	CH³OCH³ −CH-N-C- OCH⁵CH³
	839	CH-CH ₂ -	2	2	1	-	Н	-CH-N-C
20	840	CH-CH2-	2	2	1	-	н	-(CH ₂) ₃ -C-
25	841 .	CH	2	2	1		н.	-(CH ₂) ₂ -C
30	842	CHCH2-	2	2	1	-	н	-(CH ₂) ₂ -C-C
35	843	CH-CH2-	2	2	1	-	H .	-(CH ₂) ₂ -CH ₃
40	844	CH2-	2	2	1	-	н	-(CH ₂) ₂ -C-CH ₃
	845	CH- (-)-CH₂-	2	2	1	•	н	-(CH ₂) ₂ -C
45	846	C├ - CH ₂ -	2	2.	1		н	-(CH ₂) ₂ -C-C-
50	847	CH-€-	2	2	1	-	н	-(CH ₂) ₂ -C

Table 1.78

5	Compd. No.	R (CH ₂),-	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	848	CH-CH2-	2	2	1	-	н	-(CH ₂) ₂ -CH ₃
	849	CH-(-)-CH2-	2	2	1		н	-(CH ₂) ₂ -C- H ₃ CO
15	850	CH-CH2-	2	2	1	-		- CH ₂ - Ş- СН ₃
20	851	CH2−	2	2	1	-	н.	- CH2-N-C-N-CF3
25	852	CH-CH ₂ -	2	2	1	-	н.	-CH ₂ -N-C-N-CF ₃
30	* 853	CF CH₂-	2	2	1	-	Ή ˙	-сн²-йс-й-
35	854	CH-CH2-	2	2	1 ·	· -	н	-CH ₂ -N-C-N-CH ₃
	855	CH-CH ₂ -	2	2	1	-	н	- CH₂- N-C-N-(CH₃
40	856	CH-CH ₂ -	2	2	1	-	н	-CH ² -N-C-N-C-C-CH ³
45	857	CH-CH ₂ -	2	2	1	•	н	-сн₂- h с- h — Осн³
50								-CH2-HC-N- OCH3

Table 1.79

5	Compd. No.	R ¹ (CH ₂);	k	m	n	chirality	R ³	$-(CH_2)_{p} + (CH_2)_{q} - (C$
10	859	CCH₂-	2	2	. 1	<u>-</u> ·	н	-CH2-NC-H
15	860	CCH₂-	2	2	1	-	H	-CH3- H C- H CN
,5	861	C├ - CH₂-	2	2	1	-	. н	-CH2-N-C-N-
20	862	C	2	2	1	-	н	-CH2-N-C-N-C-CH3
25	863	. C├ - (CH ₂ -	2	2	1	-	Н	-CH ₂ -N-C-N-C-N-C-N-C-N-C-N-C-N-C-N-C-N-C-N-
30	864	CH-CH ₂ -	2	2	· 1	-	 Н	-CH2-N-C-N-C-N-C-OCH3
<i>35</i>	865	CH-2-	2	2	1	-	н	-CH ₂ -N-S-CH ₃
	866	C├ - CH ₂ -				-	H	- CH ₂ -N-S-CF ₃
40	867	CH-CH2-	2	2	1	-	, н	- CH ₂ -N-S
45								- CH ₂ - № \$
50	869	CH-CH₂-	2	2	1	-	н	-CH ₂ -N-S-CH(CH ₃) ₂

Table 1.80

5	Compd.	R ² (CH ₂)-	k	m	n	chirality	R³	-(CH ₂) p 5 (CH ₂) q G-R ⁶
10	870	с⊢—СН₂-	2	2	1		н _.	- CH ₂ -N-\$-
	871	С⊢—СН₂-	2	2	1	-	Н	- CH ₂ - N S (CH ₂) ₃ CH ₃
15	872	C	2	2	1	-	н	-CH2-N-S-
20	873	CH2−	2	2	1		н	- CH ₂ -N- C- O CH ₂ -
25	874	СН2-	2	2	1	-	н.	- CH O C N CI
30	875	← CH ₂ -	2	2	1		Н	-CH ₂ -N-CF ₃
35	876	Br—CH ₂ -	2	2	1	-	н .	-CH ₂ -N-C-CF ₃
	877	NC-CH ₂ -	2	2	1	-	H	-CH ₂ -N-C-CF ₃
40 _.	878	O ₂ N-CH ₂ -	, 2	2	1	<u>-</u> ·	Н	- CH ₂ -N-C-CF ₃
45	879	O O CH₂-	2	2	1	. -	н	- CH ₂ -N-C-CF ₃ - CH ₂ -N-C-CF ₃ - CH ₂ -N-C-CF ₃
50	880	O O CH2-	2	2	1	-	н	-CH ₂ -N-C-CF ₃

Table	1.81	
	1.0	

5	Compd. No.	R (CH ₂);-	k	m	n	chirality	R³	$-(CH_2)_{p} + G^4 + (CH_2)_{q} - G^-R^6$
10	881	Br CH2-	2	2	1	<u>-</u>	н	- CH2- N- C-CF3
	882	OH2-	2	2	1	-	н	-CH2-N-C-CF3
15	883	CI CH ₂ -	2	2	1	-	н	- CH ₂ - N C-CF ₃
20	884	₩ċ.c-Йαн³-	2	2	1		н	-CH2-N-C-
25	885	H3C-8- CH2-	. 2	2	1	· -	н	-CH2-N-C-CF3
30	886	F-CH ₂ -	2	2	1	-	H	-CH2-N-C-
0.5	887	F ₃ C-√CH ₂ -	2	2	1	-	н	-CH ₂ -N-C-CF ₃
35	888	HOCH₂-				-	. Н	-CH ₂ -N-C-CF ₃
40	·889 ·	CH2-	2	2	1	-	н	O CF ₃
45	890	CH2-	2	2	1	-	Н	$-CH_{2}-NC$
50	891	CI CH₂-	2	2	1	. -	н	- CH ₂ -N-C-CF ₃

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Table 1.82

5	Compd. No.	R ¹ (CH ₂)-	k	m	n	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} - (CH_2)_{q} - (CH_2)_{q}$
10	892	H₃CO ————————————————————————————————————	2	2	1	-	н	- CH ₂ -N-C-CF ₃
	893	O ₂ N CH ₂ -	2	2	1	-	н	-CH ₂ -N-C-CF ₃
15	894	HO CH ₃ H ₃ C CH ₂ - CH ₃	2	2	1	-	Н	-CH2-N-C-CF3
20	895	(CH ₂) ₂ -	2	2	1	-	н	-CH ₂ -N-C-CF ₃
25	896	CN CH₂-	2 ′	. 2	1	-	н	-CH ₂ -N-C-CF ₃
	897	HO₂C CH₂-	2	2	1	-	н	-CH ₂ -N-C-CF ₃
35	898	HO ₂ C-\(\bigcirc\)-CH ₂ -	2	2	1	• •	н	- CH ₂ - N- C-
		OCH ₃				-	н	- CH ₂ -N-C-CF ₃
40	90 <u>0</u>	н₂∞₂с-{сн₂-	2	2	1	-	н	-CH ₂ -N-C-
45	901	CH-	2	2	1	-	. н	- CH ₂ -N-C-CF ₃
50	.902	O ₂ N CH ₂ -	2	2	1	. •	н	- CH ₂ -N-C-CF ₃

Table 1.83

	Compo No.	$H \xrightarrow{R^1} (CH_2)_i -$	k	m	п	chirality	R³	—(CH ₂) _p + (CH ₂) _q G−R ⁶
	903	H ₂ CO CH ₂ - OCH ₃	2	2	1	•	н	-CH ₂ -N-C-CF ₃
	904	HO CH₂-	2	2	1	-	н	- CH ₂ - N- C-
	905	O ₂ N CH ₂ -	2	2	1		H .	-CH ₂ -N-C-CF ₃
	906	(CH ₂) ₃ -	2	2	1	-	н	- CH₂- N-C-CF3
	907	CH(CH ₂) ₂ -	2	2	. 1	-	H .	CH ₂ -N-C-CF ₃
	908	H C OH 2-	['] 2	2	1"	-	н	-CH ₂ -N-C-CF ₃
	909	Q-12°C-Q-Q+2-	2	2 .	1	-	н	-CH ₂ -N-C-CF ₃
	910	CI CH₂-	2	2	1	-	н	-CH ₂ -N-C-CF ₃
	911	CI — CH₂-	2	2	1	-	н	O CF ₃
	912	Br CH2-	2	2	1	-	н	- CH ₂ -N-C-CF ₃
	913	н₃со-{сн₂-	2	2	1	-	н	-CH ₂ -N-C-CF ₃
_			<u> </u>		··		<u> </u>	

Table 1.84

Compd. No.	R ² (CH ₂)	k	m	n	chirality	R³	—(CH ₂) _p + (CH ₂) _q G-R ⁶
914	О-0420-О-СИ4-	2	2	1	-	Н	- CH ₂ - N- C-
915	OH CHCH₂-	2	2	1	-	н	CH ₂ - N- C
916	N CH ₂ -	2	2	1	-	н	- CH₂- N-C CF3
917	CH ₂ -	2	2	1	· _	н	- CH ₂ - N- C-
918	H ₃ CO ₃ C OH ₂ -	2	2	1		н .	- CH ₂ -N-C-
919	H ₃ C-CH ₂ -	2	2	1	-	н	- CH ₂ - N- C- CF ₃
920	OCF ₃	2	2	1	-	н	- СН ₂ - N- С-
921	CH ₂ -	2	2	1	<u>.</u> ·	н	- CH ₂ -N-C-CF ₃
922	> CH₂-	2	2	1	<u>.</u> ·	н	- CH₂- N- C- CF₃
923	CH-CH-	2	2	1	-	н	- CH ₂ -N-C
924	H ₂ N-C 0	2	2	1	-	н	-CH _z -N-C-

Table 1.85

Compd.	R ² (CH ₂)	k	m	n	chirality	R³	R ⁴ −(CH ₂) _p + (CH ₂) _q G−R ⁶
925	H ₂ N-C	2	2	1	-	អ	-сн _{г н} с С С С С С С С С С С С С С С С С С С
926	CH2	2	2	1	· · · · · · ·	н	-сн ₂ -N-с-СF ₃
927	F ₃ CQ —CH ₂ -	2	2	1		н	CH ₂ -N-C
928	F3CO-CH3-	2	2	1	-	н	-CH ₂ -N-C-CF ₃
929	H₃CS	2	2	1		н	-CH ₂ -N-C-CF ₃
930	CH₃ CH₂-	2	2	1	- •	Н	-CH ₂ -N-C
931	NC CH₂-	2	2	1	-	Н	-CH2-N-C-CF3
932	CH2-	2	2	1	-	н	-CH ₂ -N-C CF ₃
933	CH- CH−	2	2	1	-	н	-CH_N-C-CF3
934	CH₂-	2	2	1	-	н	-CH2-N-C-CF3 -CH2-N-C-CF3 -CH2-N-C-CF3
935	CH ₃ -CH ₂ - CH ₂ - CH ₂ - CH ₂ -	2	2	1	-	н	-сн- N-с-СF3
						· · · · · · · · · · · · · · · · · · ·	

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Table 1.86

5	Compd.	R ² (CH ₂),	k	m	n	chirality		-(CH ₂) p (CH ₂) q G-R ⁶
10	936	NO ₂	2	2 ·	1	-	н	-CH ₂ -N-C-CF ₃
10	937	(H ₃ C) ₂ N	2	2	· 1	-	н	-CH2-N-C-CF3
15	938	CH-CH2-	2	2	1	-	н	-CH ₂ -N-C-CF ₃
20	939	O ₂ N CH ₂ -	2	2	1	-	н .	-CH ₂ -N-C
. 25	940	OH — CH₂-	2	2	1	-	. н	-CH_N-C-CF3
30	941	F ₃ G CH2-	2	2	1	- • •	· н.	-CH ₂ -N-C-CF ₃
	942	CH-CH2-	2	2	1	-	н	O CF ₃ -CH N C C CF ₃ -CH(CH ₃) ₂ CF ₃
35	943	CH-CH2	1	4	0	-	Н	-CH ₂ -N-C-CF ₃
40	944	C├─(1	. 4	0	-	н	-CH ₂ -N-C-CH ₃
45	945	CH-€	1	4	0	-	н	-CH ₂ -N-C-
50	946	C├-{CH ₂ -	1	4	0		н	-CH ₂ -N-CNO ₂
•								

Table 1.87

5	Compd. No.	R ² (CH ₂) _j -	k	m	n	chirality	Ŕ³	-(CH ₂) _p CH ₂) _q G-R ⁶
10	947	C├-{}-CH₂-	1	4	0	•	н	-(CH ₂) ₂ -N-C
	948	CH-2-	1	4	0	-	Н	-(CH ₂) ₃ -C-N-CI
15	949	с⊢С сн₂-	1	4	0	-	н	-(CH ₂) ₃ -С-N-СH ₂ -
20	950	CH2-	0	4	1		н	-CH2-N-C-
25	951.	C ⊢ CH ₂ -	1	2	0	R	H.	-сн - и с-
30	952 ·	C ⊢ CH₂-	1	2	0	R	н	-CH ₂ -N-C
	953	CH2-	1	2	0	R	н	-(CH ₂)-N-C-\-\-\-\-\-\-\-\-\-\-\-\-\-\-\-\-\-\
35	954	CH ₂ -	1	2	0	R [.]	н	-CH [≤] -N-C-NH
40	955	С⊢—СН₂-	1	2	0	R	н	-(CH ₂) ₂ -N-C- H H ₃ C-NH
45	956	CH-2-	1	2	0	R	н	-(CH ₂) ₂ -N-C
50	957	C├ ─ CH₂-	1	2	0	R	Н	-сн <u>-</u> h-с-
		· · · · · · · · · · · · · · · · · · ·						

Table 1.88

Compd.	R ² (CH ₂)	k	m	n	chirality	- R³	$-(CH_2)_p + (CH_2)_q G - R^6$
958	с⊢(Сн₂-	1	2	0	R	н	-(CH ₂) ₂ -N-C-
959	CI—(CH₂-	1	2	0	R	H	-сн ² -и-с-сн³
960	C├ - CH ₂ -	1	2	0	R	н	-(сн₂) н с-сн₃
961	CH-2-	1 ·	2	0	R	н	-сн ₂ -и-сн₃
962	Ç ⊢√ -CH₂-	1	2	0	, R	н.	-(CH ₂) ₂ -N-C- H CH ₃
963	CH-CH ₂ -	,1	2	0	R	. н	-(CH ₂) ₂ -N-СОН
964	CH-CH ₂ -	1	2	0	R	н	-CH2-N-C- H -CO2CH3
	CH-(-)-CH ₂ -						-(CH ₂) ₂ -N-C- H
966	C├ - CH₂-	1	2	0	R	н	-CH ₂ -N-C-CH ₃
967	CH₂-	1	2	0	R	н	-(CH ₂) ₂ -N-C-⟨-CH ₃
							-CH2-N-C-NH
							···

Table 1.89

5	Compd. No.	R ¹ (CH ₂) _j -	k	m	n	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} - G-R^6$
. 10	969	С├-{СН₂-	1	2	0	R	н	-(CH ₂) ₂ -N-C-NH
	970	CI—CH₂-	1	2	0	R	н	-CH ₂ -N-C-\(\sigma\) N(CH ₃) ₂
15	971	CH-CH ₂ -	1	2	0	R	H	-(CH ₂) ₂ -N-C-N(CH ₃) ₂
20	972	C├ - CH ₂ -	1	2	0	R	н	-CH2-N-CNH2
25	973 .	сн-СН ₂ -	1	2	0	R	н <u>.</u>	-(CH ₂) ₂ -N-C-
<i>30</i>	974	с⊢—СН₂-	1	2	0	R	н	-CH ₂ -N-C
	975	СН-СН₂-	1	2	0	R	н	-(CH ₂) ₂ -N-C-NH ₂
35	976	CH-CH ₂ -	1	2	. 0	R	H	-сн²-и-с- В
40	977	CH_CH ₂ -	1	2	0	R	н	-(CH ₂) _Z -N-C-NH
45	978	CH-2-	1	2	0	R	н	-CH ² -N-C
50	979	с⊢—СН₂-	1	2	0	R	н	-(CH ⁵) ² -H-C-NH

Table 1.90

5	Compd. No.	R (CH ₂)	k	m	n	chirality	R³	$-(CH_2)_{\overline{p}} + (CH_2)_{\overline{q}} G - R^6$
10	980	C├ - CH₂-	1	2	0	R ·	н	-CH2-N-C-CH3
	981	CI-CH ₂ -	1	2	0	R	н	-(CH2)2-N-C-CH3
15	982	С⊢-{	1	2	Ó	R	H	-CH ₂ -N-C
20	983	CH-2-	1	2	0	R		-(CH ₂) ₂ -N-C- (H ₃ C) ₂ N
25	984	,CH-CH ₂ -	1	2	0	R	н.	-CH ₂ -N-C
30	985	CH2-	1	2	o .	R	н	-(CH ₂) ₂ -N-С-СН ₂ ОН
ar.	986	CH CH	1	2	0	R ·	н :	-CH ₂ -N-C-CF ₃
35	987	CH-CH₂-	2	2	1	- ,	H	-CH ₂ -N-C-CF ₃
40		CH-CH2-				•	н	-CH2-N-C-CF3
45	989	CH-CH2-	1	4	0	-	н	-CH ₂ -N-C-O-CH ₂ -
50	990	CH-CH₂-	· 1	4	0	-	н 	-CH ² -H-C-

Table 1.91

5	Compd. No.	R ² (CH ₂)	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	991	CH-CH2-	1	4	0	-	н	-(CH ₂) ₂ -C-
	992	CH-€ CH ₂ -	1	4	0	•	н	OCH ₃
15	993	CH ₂ -	1	4	0	-	н	-(CH ₂) ₂ -C
20	994	CI————————————————————————————————————	1	4	0	-	н	-(CH ₂) ₃ -C-
25	995	CI—(CH₂-	1	4	0	· .	н	-(CH ₂) ₃ -C
30	996	CI-CH ₂ -	1	4	0	<u>.</u> .	н	-(CH ₂) ₃ -C-N-CH ₃
	997	CH-CH ₂ -	2	2	1	-	н	- CH N- C
35	998	CH-€T-CH ₂ -	2	2	1	-	н	CH2CH(CH3)2
40	999	CHCH ₂ -	2	2	1	-	н	-CH ₂ CH ₂ CH ₃
45	1000	CH-CH₂-	2	2	1	•	н	OH2CH(CH3)2
50	1001	CH-€-	2	2	1	-	Н	-CH-N-C

Table 1.92

5	Compd.	R ¹ (CH ₂),	k	m	n	chirality	⁻ R³	$-(CH_2)_{p}$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
10	1002	С⊢-СН₂-	2	2	1	-	н	O OCF3 -CHN-C
	1003	CH-€-CH₂-	2	2	1	-	н	O -CHN-C- H CH2CH(CH)2
15	1004	CI—CH₂-	2	2	1	- ·	H	CH ² CH(CH ³) ² OCH ³
20	1005	CH-CH ₂ -	2	2	1		н	-CH ² CH(CH ²) ² CH ³
25 .	1006	CH-CH ₂ -	2	2	1	• .	Н -	OH ³ CH(CH ³) ⁵ OCH ³ CH ³ OCH ³ CH ³
30	1007	CH_CH ₂ -	2	2 .	1	-	н	ОН ³ СН(СН ³) ³ ОСН ³ СН ³
	1008	CH-CH ₂ -	2	2	1	-	H	(CH2)2-C-NH2
35	1009	CH-2-	2	2 ·	1	-	н	(CI45) & C-NH2 -CH-N-C-(2)
40	1010	C├────────────────────────────────────	2	2	1	-	н	(CH2) = G-NH2 (CH2) = G-NH2 (CH2) = G-NH2 (CH2) = G-NH2
45	1011	CH-CH ₂ -	2	2	1	-	. H	- CH ² CH ² CH ³
50	1012	CH-₹	2	2	1	-	н	CH ₂ CH ₃ -CH ₁ CH ₂ CH ₃ -CH ₂ C-NH ₂ -CH ₂ C-NH ₂ -CH ₃ C-NH ₂ CCH ₃
•								

Table 1.93

Compd. No.	R ² (CH ₂);	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶ R ⁵
1013	C-CH ₂ -	2	. 2	1	-	н	- CH-N-C
1014	CH-CH ₂ -	2	2	1	-	H	-CHN-C
1015	С⊢-{СН₂-	2	2	1	-	н	(CH2)2-G-NH2 OCH2CH3
1016	C├ - CH₂-	2	2	0	-	H	-CH2-N-C-CF3
1017	CH-{	. 2	2	0 ·	-	н	-сн _{2-й-с} -
1018	CI—CH₂-	. 2	2	- 1	-	н	OCH ₂ CH ₃
1019	CH-CH2-	2	2	1	-	н	-сн₂-N-С- Осн₂сн₃ Осн₂сн₃
1020 [°]	CH-CH2-	2	2	1	<u>.</u>	н	-CH ₂ -N-C
1021	CH_CH ₂ -	. 2	2	1	-	Н	OCH ₂ CF ₃ -CH ₂ -N-C
1022	C├ - CH₂-	2	2	1	-	Н	CH3 OCH3
1023	CH-{-}-CH2-	2	2	1	-	н	(5) P CH ₂ CH ₃ -CH-N-C-CH ₂ CH ₃
							

Table 1.94

Compd. No.	R ¹ (CH ₂)-	k	m	n	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} G - R^6$
1024	C├ - CH ₂ -	2	2	1	•	н	(S) Q OCH ₃ -CH ₃ OCH ₃ OCH ₃
1025	CH ₂	2	2	1	-	н	(S) P OCH₂CH₃ -CH₃ CH₃ -CH3
1026	CH-CH ₂ -	2	2	1	-	н	(S) OCH ₂ CH ₃ -CH-N-C
1027	CH-CH ₂ -	2	2	1	-	н	(3) OCH3CH3
1028	CH-CH2-	2	2	1	<u>.</u> .	н	(S) OCH ₂ CF ₃ -CH-N-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-
1029	CI—CH₂-	2	2	1	-	н	(S) O OCH ₂ CH ₃ -CH-N-C-
1030	CH-CH₂-	2	2	1	· · · · · · · · · · · · · · · · · · ·	н	(S) POCF ₃ -CHN-C-CH ₃
1031	C├ - CH ₂ -	2	2	1	- .	н	(S) POCH ₃ -CH-N-C-C
1032	CH-CH2-	2	2	1	-	н	(A) OCH3 -CH-N-C- CH3 CH3 OCH3
1033	CH-CH₂-	2	2	1	-	H	(F) P CH ₂ CH ₃ -CH-N-C-CH ₂ CH ₃ CH ₃
1034	CH-CH ₂ -	2	2	1	-	н	(H) POCH3 -CH3 OCH3

Table 1.95

5	Compd.	R ¹ (CH ₂)j-	k	m	n	chirality	R ³	$-(CH_2)_{p} + \frac{R^4}{R^5} (CH_2)_{q} - G - R^6$
10	1035	CH-(-)-CH2-	2	2	1	-	н	(F) OCH ₂ CH ₃ -CH-N-C
15	1036	с⊢— сн₂-	. 2	2	1	-	н _.	(A) -CH-N-C → OCH ₂ CH ₃ -CH ₃ OCH ₂ CH ₃
.5	1037	CH-2-	2	2	1	-	Н	(A) OCH2CH3 -CH-N-C
20	1038	CH2-	2	2	1	-	н	(A) OCH ₂ CF ₃ -CH-N-C-(-) -CH-N-C-(-) -CH ₃ OCH ₂ CF ₃
25	1039	CH-CH ₂ -	2	2	1.	-	н	(A) OCH ₂ CH ₃ -CH-N-C .
30	1040	C	2	2	1	•• •	н	(A) P OCF3 -CHN-C-CH
35	1041	CH-CH2-	2	2	1	-	. н	(A) D OCH3 -CH-N-C-CH3 CH3
40	1042	CH-2-	2	2	1	. .	н .	-CH ₂ -N-C
	1043	CH2-	2	2	1		н	-CH ₂ -N-C
45	1044	CH		2			н	-CH ₂ -N-C
50	1045	CH-CH₂-	2	2	1	-	н	$-CH_{2}-N-C$ $+L_{2}N$ $-CH_{2}-N-C$ $+L_{2}N$ $-CH_{2}-N-C$ $+L_{2}N$
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Table 1.96

Compd.	R ² (CH ₂)	k	m	n	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} G - R^6$
1046	с⊢—СН₂-	2	2	1	-	н	-CH ₂ -N-C
1047	C├ ~ CH₂-	2	2	1	-	н	-CH ₂ -N-C-CH ₃
. 1048	CH-CH2-	2	2	1	-	н	-сн ₂ -N-с- + н ₂ N ОСН ₃
1049	CH-CH2-	2	2	1	-	н	-CH ₂ -N-C- H ₂ N Br
1050	CI—CH₂-	. 2	2	1.	-	н	(S) Q OCH ₃ -CH-N-C- OCH ₃ CH ₂ CH(CH ₃) ₂ OCH ₃
1051	CH2−	.5	2	·1		· H·	(5) Q CH ₂ CH ₃ -CH-N-C-CH-CH ₃ CH ₂ CH(CH ₃) ₂
1052	CH-€	2	2	1	-	н	(S) Q OCH ₃ -CH-N-C- OCH ₃ -CH ₂ CH(CH ₃) ₂ OCH ₃
1053	CH-CH2-	2	2	1	-	н	(5) OCH ₂ CH ₃ -CH-N-C
1054	CHCH2-	2	2,	1		H .	(S) OCH ₂ CH ₃ -CH-N-C
1055	C⊢CH₂-	2	2	1	· -	н	(5) P OCH ₂ CH ₃ -CH-N-C- OCH ₃ -CH ₂ CH(CH ₃) ₂
1056	CH-(CH₂-	2	2	1	· -	н	(S) OCH ₂ CF ₃ -CH-N-C- H CH ₂ CH(CH ₃) ₂ OCH ₂ CF ₃

Table 1.97

5	Compd. No.	R ¹ (CH ₂)	k	m	n	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} - G - R^6$
10	1057	C├ - CH ₂ -	2	2	1	- .	· H	(A) OCH2CH3 -CHN-C
	1058	CH-CH2-	2	. 2	1	-	н	(S) P OCH ₃ -CH-N-C- CH H CH ₂ CH(CH ₃) ₂
15	1059	C ├── CH ₂ -	2	2	1	-	н	(S) O OCF ₃ -CH-N-C
20	1060	CI—CH₂-	2	2	1	-	н	(A) O OCH2CH3 -CH-N-C OCH3 -CH2CH(CH3)2
25	1061	C├ - CH ₂ -	2	2	1		н .	(A) OCH2CF3 -CH-N-C- H CH2CH(CH3)2 OCH2CF3
30	1062	C├ - CH ₂ -	2	2	-1		• • н	(5) P OCH ₂ CH ₃ -CH-N-C
35	1063	CH-€	2	2	1	-	н	(F), Q −CH-N-C- CH ₂ CH(CH ₃) ₂
	1064	с⊢С≻сн₂-	2	2	1	-	н	(F) OCF ₃ -CH-N-C- H CH ₂ CH(CH ₃) ₂
40	1065	C├ - CH ₂ -	2	2	1	-	н	(A) P OCH3 -CH-N-C- CH2CH(CH3)2 OCH3
45	1066	C ├── CH₂-	2	2	1	-	н	(A) CH2CH2 -CH-N-C-C CH2CH(CH3)2
50	1067	C├ ~ CH₂-	2	2	1	-	н	(A) OCH3 -CH-M-C

Table 1.98

5	Compd. No.	R ¹ (CH ₂) _j -	k	m	n	chirality	· R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1068	C├ - CH ₂ -	2	2	1	•	н	(A) OCH2CH3 -CH-N-C- OCH2CH3 CH2CH(CH3)2
	1069	CH-{}-CH₂-	2	2	1	-	н	(A) OCH2CH3 -CH-N-C CH2CH3 CH2CH(CH3)2 OCH2CH3
15	1070	C├───────────────────────	2	2	1	-	н	CH2OCH2
20	1071	. C├ - CH₂-	2	2	1	-	н	-CH-N-C
25 •	1072 ·	CH2−	2	2	1	·	н	-CH-H-C-C(CH3)3
30	1073	CH-CH₂-	2	2	··· 1 ·	<u>-</u>	н ·	O120 CH2
	1074	CH₂-	2	2	1	-	н	- CH N C - C O O O O O O O O O O O O O O O O O
33	1075	CH-CH2-	2	2	1	-	н	- CH H C CH2 CH2 CH2 CH2 CH2 CH2 CH2 CH2
40	1076	CH-CH ₂ -	2	2	1	-	н	OH20 CH2-
45		CH-CH ₂ -						CU ACU -/ \
50	1078	CHCH2-	2	2	1	•	н .	-CH-N-C-
			 .				· ————	

Table 1.99

5	Compd.	R ² (CH ₂) _j	k	m	n	chirality	· R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
	1079	CHCH ₂ -	2	2	1	-	• н	-CH-N-C
10	1080	CH-CH2-	2	2	. 1	-	н	O+20CH2CH2
15	1081	с⊢—Сн₂-	2	2	1	-	Н	Of OCH?
20	1082	CH-CH2-	2	2	1	-	н	(5) P C C C C C C C C C C C C C C C C C C
25	1083	CH-CH ₂ -	2	2	1	-	Н	(A) P O O
30	1084	CHCH2-	1	2	0	R	н	-CH ₂ -N-C-
	1085	CI—CH₂-	1	2	0	R	н	-CH ₂ -N-C-NO ₂
35	1086	CH-{	1	2	0	R.	н	-CH ₂ -N-C-
40		CH-CH2-						-CH ₂ -N-C-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-
45	1088	CH-CH2-	1	2	0	R	н	-CH ₂ -N-C
50	1089	CH—CH₂-	1	2	0	R	н	-CH ₂ -N-C-N-H

Table 1.100

5	Compd. No.	R ¹ (CH ₂)	k	m	n	chirality	R³	$-(CH_2)_p$ $+ \frac{R^4}{R^5}$ $(CH_2)_q$ $G-R^6$
10	1090	с⊢—СН₂-	1	2	0	R	н	-CH ₂ -N-C
	1091	С├-{СН₂-	1	2	0		н	-CH ₂ CH ₂ -N-C
15	1092	CH-CH2-	1	2	0	R	н	-CH ₂ CH ₂ -N-C
20	1093	CH-CH ₂ -	1	2	0	R .	н	-CH ₂ CH ₂ -N-C
25	1094 [.] •	CH-(-)-CH ₂ -	1	2	0	R	н.	-CH2CH2-N-C-N-H
30	1095	CH2-	1	2	0	R	· Н	-CH ₂ CH ₂ -N-C-
	1096	CH-CH ₂ -	1	2	0	R	н	-CH ₂ CH ₂ -N-C-N-N-H
<i>35</i>	1097	CHCH ₂ -	· 1	2	0	R	н	-CH2CH2-N-C-
40	1098	CH-CH ₂ -	1	2	0	R	н	−CH ₂ −N-C−−−CH ₃
45	1099	C├ - CH₂-	1	2	0	R	н	-CH₂-N-C
50	1100	CH-CH2-	1 -	2	0	R	н	-CH ₂ -N-C

Table 1.101

5	Compd. No.	R ¹ (CH ₂)	k	m	n	chirality	[*] R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1101	CH-2-	1	2	0	R	н	-CH2-N-C
15	1102	с⊢—СН₂-	1	2	0	R	. н	-CH ₂ -N-C-NO ₂
	1103	H₃C-€ CH₂-	1	2	0	R	н	-CH ⁵ -N-C- BL
20	1104	H ₃ C-{ CH ₂ -	1	2	0	R	н .	-CH⁵-M-C
25	1105	H ₃ C-CH ₂ -	1	2	0	R	н .	-CH ₂ -N-C
30	1106	H ₃ C-√2-CH ₂ -	· ·1	2	. 0	R	H-	-CH ₂ -N-C
35		Н ₃ С-СН ₂ -					н	-CH ₂ -N-C-CH ₃
40		CH ₃ CH ₂ - CH ₃					н	н
	1109	CH ₃ CH ₂ - CH ₃	1	2	0	R	н	-CH ₂ -N-C
45	1110	CH ₃ CH ₂ CH ₃	1	2	O.	R	Н	-CH ₂ -N-C
50	1111	CH ₃ CH ₂ −	1	2	0	R	Н	$-CH_{2}-N+C$

٦	73	h	le	1	1	n	2
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5	Compd. No.	R ² (CH ₂)	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1112	CH ₃ CH ₂ - CH ₃	1	2	0	R	H	-CH ₂ -N-CNO ₂
	1113	CH_CH2	2	2	1	-	н	-CH2-N-C
15	1114	CH-CH2-	2	2	1	-	н	-CH ₂ -N-C
20	1115	CH-CH ₂ -	2	2	1	-	н	-сн ₂ -ү-с СI
25	1116	CH2-	2	2	1	· -	н	-CH2-N-C
30	1117	CH-CH ₂ -	2.	2	1	-	н	-CH ₂ -N-CNO ₂
35	1118	Chicago Cota	1	2	0	R	H	-CH ₂ -N-C-CF ₃
,	1119	H ₃ CS-CH ₂ -	1	2	0	R	H	-CH2-N-C-CF3
40	1120	H ₃ CQ CH ₂ - OCH ₃	1	2	. 0	R	Н	-сн ₂ - № с
45	1121	H ₃ C O ₂ N CH ₂ -	1	2	0	R	н	-CH₂-N-C-
50	1122	H ₂ C (H ₂ C) ₂ CH- CH(CH ₂) ₂	1	2	0	R	H,	-CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃

Table 1.103

5	Compd. No.	R ¹ (CH ₂);	k	m	n	chirality	. 'R ₃	$-(CH_2)_{p} + (CH_2)_{q} G - R^6$
10	1123	CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
	1124	O ₂ N O CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
15	1125	с⊢—СН₂-	2	2	1	-	н	-a+N-c
20	1126	C├ - CH ₂ -	2	2	1	· -	н	-CH-N-C
25	1127	CH√CH _Z -	2	2 .	1	-	н	-CH-N-C-NH
30	1128	с⊢—Сн₂-	2	2	. 1	. ·	н	-CH-NC-CF3
35	1129	CH2-	2	2	1	-	н	-CH-NG-CF3
	1130	с⊢— СН₂-	2	2	1		н	-CHNC-
40	1131	с⊢—СН₂-	2	2	1	• -	н	O-LOCHT
45	1132	С⊢—СН₂-	2	2	1	-	. н	-CH-NC-CF3
50	1133	H ₃ CO CH ₂ -	1	. 2	0	R	н	-CH2-N-C-CF3
•						_		•

Table 1.104

5	Compd. No.	R ¹ (CH ₂);-	k	m	n	chirality	R³	-(CH ₂) p G (CH ₂) q G-R ⁶
10	1134	H ₃ CO CH ₂ - H ₃ CO	1	2	0	R	н	-CH ₂ -N-C-CF ₃
	1135	CH ₂ - NO ₂	1	2	0	R	н	-CH ₂ -N-C-CF ₃
15	1136	CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
20	1137	CH₂-	1	2	0	R	н	-CH ₂ -N-C-CF ₃
25	1138	CH ₂ -	.1	2	0	R	н	-CH ₂ -N-C-CF ₃
30	1139	(CH ₂) ₂	··1	2	0.	R	н	-CH ₂ -N-C-CF ₃
35	1140	O ₂ N — CH ₂ -	1	. 2	0	R	н	-CH ₂ -N-C-CF ₃
	1141	CH ₂ -					н	-CH ₂ -N-C-CF ₃
40	1142		1	2	0	R	н	-CH ₂ -N-C
45	1143	O-otto-CHT	1	2	0	, R	н .	-CH2-N-C-CF3
50	1144	H₃CO H₃CO	1	2	0	R	Н	-CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃

Table 1.105

5		R ¹ (CH ₂) _j					R ³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1145	H ₃ CO CH ₂ -	1	2	0	R	H	-CH ₂ -N-C-CF ₃
	1146	O+,O-(CH2-	1	2	0	R	н	-сн ₂ -N-с-СF ₃
15	1147	40-c-H > OHE	1	2	0	R	н	-CH ₂ -N-C-CF ₃
20	1148	-CH₂-	1	2	0	R	н	-CH ₂ -N-C-CF ₃
25	1149	CH ₃ CH ₂ -	1	2	0	R	н	-CH2-N-C
30	1150	CH ₃ CH ₂ - CH ₃	1	2 ·	0	R	н	-CH ₂ -N-C-CH ₂ CH ₃
<i>35</i> -	1151	CH ₃ CH ₂ CH ₃					н	-CH ₂ -N-C-CH ₂ CF ₃
	1152	CH₃ N CH₂- CH₃	1	2	0	R	н	-CH2-N-C-N-F
40	1153	CH ₃	1	2	0	R	H .	-CH ₂ -N-C-H
45	1154	CH₃ N CH₂- CH₃	1	2	0	R	н	-CH ₂ -N-C-N-CH ₃
50	1155	CH ₃ CH ₂ -	1	2	0	R	H .	H -CH ₂ -N-C-CH ₃ F ₃ C

Table 1.106

Compd. No.	R ¹ (CH ₂)	k	m	n	chirality	. K3	-(CH ₂) , C CH ₂) G-R ⁶
1156	CH ₃ CH ₂ -	1	2	0	R	. н	-CH ₂ -N-C-(CH ₃) ₃
1157	CH ₃ N CH ₂ - CH ₃	1	2	0	R	H	-CH2-NC-SSCH3
1158	CH₃ CH₃	1	2	0	R	н	-CH ₂ -N-C
	CH₃ CH₃			•	•	н	$-CH_2-N-C \longrightarrow OCH_3$ $+_2N OCH_3$
1160	CH ₃ CH₂− CH₃	1	2	. 0	R	н	-CH ₂ -N-C
1161	OH -CH ₂ -	1	2	0	. R	H	-CH ₂ -N-C-CF ₃
1162	СН ₃ Н ₃ СО————————————————————————————————————	1	2	0	R	н	-CH ₂ -N-C-CF ₃
1163	H3CO-CH2-	1	2	0	R	н	-CH₂-N-C-CF₃
	H ₃ C H ₃ CO————————————————————————————————————						-CH ₂ -N-C
1165	CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
1166	Br H₃CO—CH₂-	1	2	0	R	ŀН	-CH ₂ -N-C-CF ₃

Table 1.107

Compd. No.	R ² (CH ₂),	k	m	n	chirality	⁻ R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
1167	с⊷(сн₂-	2	2	1		н	-CH2-N-C-
1168	CL N CH2-	1	2	0	R	н	-CH ₂ -N-C-CF ₃
1169	н С-С-12- 0 s — СН2-	1	2	0	R	н .	-CH ₂ -N-C-CF ₃
1170	H N CH ₂ -	1	2	0	R	н	-CH2-N-C-CF3
1171	CHCH2-	1	2	0	Ŗ	н	-сн ₂ -м-с-(Сн ₃
1172	CH-CH ₂	1	.2	0	. R	н	-CH ₂ -N-C-N-C-N-H
1173	с{СН-	1	2	0.	R	н	-CH2-N-C-NH OCH3
1174	CH-CH2-	1	2	0	R	н	-CH ₂ -N-C
1175	H ₃ C-CH ₂ -	1	2	0	R .	Н	−CH ₂ −N-C− H Br
1176	H ₃ C-CH ₂ -	1	2		R	Н	-CH ₂ -N-C-N-C-N-CH ₃ -CH ₂ -N-C-N-C-N-C-N-C-N-C-N-C-N-C-N-C-N-C-N-
1177	H ₃ C	1	2	0	R.	н	-CH₂-N-C-N-CH3

Table 1.108

5	Compd.	R ¹ (CH ₂)	k	m	'n	chirality	R³	—(CH ₂) p (CH ₂) q G−R ⁶
10	1178	H ₃ C-⟨}-CH ₂ -	1.	2	0	R	н	-CH ₂ -N-C
15	1179	н₃С-{	1	2	0	R	н	-CH ₂ -N-C-NO ₂
	1180	H ₃ C-CH ₂ -	1	2	0	R	н	-CH2-HC-NH
	•	CH ₃ N CH ₂ - CH ₃					н	-CH ₂ -N-C-Br
25		C1.13						-CH ₂ -N-C-N-C-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-
30	1183	CH ₃ CH ₂ -	1	2	. 0	R ·	. н	-CH2-N-C-N-CH3
35		CH ₃ CH ₂ − CH ₃						-CH ₂ -N-C
40	1185	CH₃ CH₂− CH₃	1	2	0	R	Н	-CH ₂ -N-C
	1186	CH ₃ CH ₂ - CH ₃	1	2	0	R	Н	-CH ₂ -N-C-N-C-N-H
45	1187	C├ - CH ₂ -	2	2	1	-	н	-CH3-M-C-CH3
50	1188	C├ - CH ₂ -	2	2	1	-	Н	-CH ₂ -N-C

Table 1.109

5	Compd. No.	R ¹ (CH ₂);	k	m	n	chirality	R³	-(CH ₂) p (CH ₂) q G-R ⁶
10	1189	с⊢(2	2	. 1	-	н	-CH ₂ -N-C-N-C-N-OCH ₃
	1190	CH-{	2	2	1	-	н	-CH ₂ -N-C
15	1191	CH₃ CH₂-	1	2	0	R	Ħ	-CH ₂ -N-C-CF ₃
20	1192	CH₃ CH₂-	1	2	0	R	н	-CH ₂ -N-C-F
25	1193	CH ₃	1	2	0	R	. н	-CH₂-N-C
30	1194	CH₃ N CH₂-	1	2	0	R	Н	CF ₃ -CH ₂ -N-C
35	1195	CH ₃ CH ₂ - CH ₃	1	2	0	R	н	-CH₂-N-C
40	1196	CH ₃ CH ₂ - CH ₃	1	2	0	R	Н	-CH2-N-C
45	1197	CH ₃ N→CH ₂ - CH ₃	1	2	0	R	н	-CH ₂ -N-C-CF ₃
40		CH ₃ N→CH ₂ - CH ₃					н	-CH2-N-C- CI
50		CH ₃ CH ₂ CH ₃					н	F -CH ₂ -N-C-CH ₃ -CH ₂ -N-C-CH ₃
55		01.13						

Table 1.110

Compd.	R 1 (CH ₂)j-	k	m	n	chirality	R³	-(CH ₂) p CH₂ G-R⁶ CH₂ CH
1200	CH ₂ -CH ₂ -CH ₃	1	2	0	R	Н	-CH2-N+C-CI
1201	CH₃ CH₃	1	2	0	R	Н	-CH ₂ -N-C
	CH₃ N CH₂- CH₃					н	-CH₂-N-C-CF3
1203	H ₃ C-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-OCF ₃
.1204 -	H ₃ C-(-)-CH ₂ -	1	2	0	R	Н,	-CH ₂ -N-C-CF ₃
1205	H ₃ CCH ₂ -	. 1	2	0	. R	н	-CH₂-N-C-S
1206	H ₃ C-CH ₂ -	1	2	0	R	н	-CH2-N-C
1207	H3C-CH2-	1	2	0	R	н	-CH₂-N-C-CF₃
1208	H ₃ C	1	2	0	R	н	-CH2-N-C-
1209	H ₃ C	1	2	0	R	н	-CH ₂ -N-C-\ -CH ₂ -N-C-\ -CH ₂ -N-C-\ -CH ₃
1210	H₃C(CH₂-	1	2	0	R	н	-CH ₂ -N-C- CI
							

Table 1.111

5	Compd. No.	R ² (CH ₂)j	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1211	H ₃ C-⟨□}-CH ₂ -	1	2	0	R	н	-CH ₂ -N-CF
15	1212	H ₃ C⟨}-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
	1213	сн-Сн-	2	2	1		н	-CH ₂ -N-C- F ₃ C
20	1214	C	2	2	1	-	н	-CH ₂ -N-C
25	1215	CH-CH2-	2	2	1	-	н	-CH ₂ -N-C- CI
30	1216	CH-2	2	2	-1	· • · ·	H	-CH ₂ -N-C
35	1217	сн-СН2-	1	2	0	R	н	-CH ₂ -N-C-CF ₃
40	1218	CH2-	1 .	2	0	R		-CH ₂ -N-C- F
45	1219	CH2-	1	2	0	R		-CH ₂ -N-C- H
	1220	CHZ-	1	2	0	R	н	-CH2-N-C-
50	1221	СҢСН₂-	1.	2 .	0	R	н	-CH ₂ -N-C-F
55								

Table 1.112

5	Compd. No.	R ¹ /(CH ₂)j-	k	m	n	chirality	R³	-(CH ₂)p + (CH ₂)q G-R ⁶
10	1222	С⊢СН₂−	1	2	0	R	Н	-CH₂-N-C-N-CH₃
15	1223	СН-СН2-	1	2	0	R	н	-CH ₂ -N-C-
75	1224	с⊢СН₂-	1	2	0	R	Н	-CH ₂ -N-C
	1225	H ₃ C-CH ₂ -	1	2	0	R	Н	-CH ₂ -N-C-CF ₃
25	1226	H ₃ C-(-)-CH ₂ -	1	2	0	R	н	CH ₂ -N-C
30	1227	H ₃ C	·1	2	0	- · R	Н	-CH ₂ -N-C-CI
35	1228	H ₃ C-CH ₂ -	1	2 -	0	R	н	-CH ₂ -N-C
40	1229	H ₃ C-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
45	1230	H ₃ CCH ₂ -	1	2	0	R		H ₂ N CH ₃ CH ₂ -N-C-N H H
50	1231	H ₃ C-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-
	1232	H ₃ C-CH ₂ -	1	. 2	0	R	н	-CH ₂ -N-C
55						<u> </u>		

Table 1.113

5	Compd.	R ² (CH ₂)j-	k	m.	n	chirality	R³	$-(CH_2)_{\overline{p}} + (CH_2)_{\overline{q}} - (CH_2)_{\overline{q}} - R^6$
10	1233	CH ₃ CH ₂ CH ₃	1	2	0	R	н	-CH2-N-C-CF3
15	1234	CH ₃ CH₂-	1	2	0	R ·	н	-CH ₂ -N-C-CH ₃
	1235	CH ₃ CH ₂ - CH ₃	1	2	0	R	H	-CH2-N-C-CI
20	1236	CH ₃	1	2	0	R	н	-CH ₂ -NC
25	1237	CH ₃ CH ₂ - CH ₃	1	2	0	R	н	-CH ₂ -N-C-F
30	1238	CH ₃ CH ₂ - CH ₃	1	2	0	-R	H	-CH ₂ -N-C-N-H
35	1239	CH ₃	1	2	0	R	н	-CH2-N-C-
40	1240	CH3	1	2	0	R	Н	-CH ₂ -N-C- HO
45	1241	CH_CH2-	2	2	1	<u>-</u>	н	-CH ₂ -N-C-CF ₃
40	1242	CHCH2-	2	2	1	-	н	-CH ₂ -N-C
50	1243	CH_CH2-	2	2	1	-	н	-CH2-N-CCI
55								

Table 1.114

5	Compd.	R ¹ (CH ₂)j-	k	m	n	chirality	Ř³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1244	с⊷(2	2	1	•	н	$-CH_2-N C \longrightarrow H_2N$
15	1245	C├ - CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
	1246	CH2-	2	2	1	-	н	-CH ₂ -N-C-\N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-
20	1247	с⊢СН₂-	2	2	1	•	н	-CH2-N-C-
25	1248	с⊢—СН₂-	.2	2	1	-	Н	-CH2-N-C
30	1249	с⊢—СН₂-	1	2	. 0	R	н :	-CH ₂ -N-C
35	1250	H ₃ C-CH ₂ -	1	2	0	R	н	-CH2-N-C
40	1251	CH ₃ CH ₂ CH ₃	1	2	0	R	н	-CH ₂ -N-C
	1252	CH2-	1	2	0	. R	н	-CH ₂ -N-C-CH(CH ₃) ₂
45	1253	H₃C-CH₂-	. 1	2	0	R	н	-CH ₂ -N-C
50	1254	CH ₃ CH ₂ - CH ₃	1	2	0	R	н	-CH ₂ -N-C
55								

Table 1.115

5	Compd.	R ² (CH ₂) _j	k	m	n	chirality	R³	$-(CH_2)_{p} + \frac{R^4}{R^5} (CH_2)_{q} - G - R^6$
10	1255	С⊢√_СН2-	1	2	0	R	н	-CH ₂ -N-C
45	1256	H ₃ C-CH ₂ -	1	2	0	R	. н	-CH ₂ -N-C
15	1257	CH ₃	1	2	0	R	н	$-CH_2-N-C\longrightarrow H_2N$
20	1258	H ₃ C-CH ₂ -	1	2	.0	R	н	-CH ₂ -N-C-
25	1259	CH₃ CH₃-	1	.2	O	R	н	-CH ₂ -N-C-
30	1260	H ₃ C-CH ₂ -	. 1	2	0	R	н	-CH ₂ -N-C-CH ₂ CH ₃
35	1261	СН-СН2-	1	2	0	R	. н	-CH ₂ -N-C-C(CH ₃) ₃ H ₃ C
40	1262	H ₃ C-CH ₂ -	1	2	0	R	Н	-CH2-N-C-(CH3)3
	1263	CH ₃ CH ₃	1	2	0	R	Н	-CH ₂ -N-C
45	.1264	С⊢—СН₂-	. 1	2	0	R	н	-CH2-N-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-
50	1265	H ₃ C-CH ₂ -	1	2	0	R	н	-CH ₂ -NC-CH
55								· · · · · · · · · · · · · · · · · · ·

Table 1.116

Compd. No.	R ¹ (CH ₂) _j	k	m	n	chirality	R ³	-(CH ₂) _p + (CH ₂) _q G-
1266	CH ₃	1	2	0	R	Н	-CH2-NC0 HC
1267	CHŹ-CHŹ-	1	2	0	R	н	-CH2-N-C-NH
1268	C⊢-(CH₂-	1	2	0	R	н	-CH2-N-C- H3CO
1269	C-CH2-	1	2	0	R	Н	-CH ₂ -N-C
1270	C├ - CH ₂ -	1	2 .	0	R	н	-cH₂-N-c-\
1271	C├ - CH₂-	1	2	0.	R	н	-CH ₂ -N-C-F
1272	H ₃ C-CH ₂ -	1	2	0	R	н	-CH2-N-C-NHCO
	H ₃ C-CH ₂ -						-CH ₂ -N-C
1274	H ₃ C-⟨	1	2	0	R	н	-CH₂-H-C
1275	H ₃ C-CH ₂ -	1	2	0	R .	H .	-CH₂-N-C- HO
1276	H ₃ C-(-)-CH ₂ -	1	2	0	R	н	-CH2-N-C

Table 1	•						· · · · · · · · · · · · · · · · · · ·
Compd.	R ² /					[:] R³	-(CH ₂) _p + (CH ₂) _q G-R
1277	CH ₃	1	2	0	R	Н	-CH ₂ -N-C-N-C-N-H-H-H-H-H-H-H-H-H-H-H-H-H-H-H
1278	CH ₃ CH ₂ - CH ₃	1	2	0	R	н	-CH ₂ -N-C
1279	CH ₃ N CH ₂ -	1	. 2	0	R	н	-CH ₂ -N-C
1280	CH ₃ CH ₂ -	1	2	0	R ·	н	-ch²-h-c- Ho Ho CI
1281	CH₃ N—CH₂- CH₃	1	. 2	0	, R	н	-CH ₂ -N-CF
1282	CH_CH_	2	2	1		. н	-CH2-N-C-N-C-N-C-N-C-N-C-N-C-N-C-N-C-N-C-N-
1283	CH_CH2	2	2	1	-	H	-CH ₂ -N-C
	с⊢С-сн₂-						-CH ₂ -N-C
1285	C├────────────────────────────	2	2	1	-		-CH ₂ -N-C
1286	H ² ¢	1	2	0	R	н	-CH ₂ -N-C-CF ₃
1287	O ₂ N-CH ₂ -	1	2	0	R	н	-CH2-N-C-CF3

Table 1.118

Compd. No.	R ² (CH ₂),	k	m	n	chirality	R³	—(CH ₂) p G (CH ₂) q G−R ⁶
1288	HQ H ₃ CO—CH ₂ -	1	2	0	R	н	-CH2-N-C-
1289	CH₃ CH₂-	1	2	0	R	н	-CH ₂ -N-C
1290	CH ₃ CH ₂ - CH ₃	1	2	0	R	н	-CH ₂ -N-C
1291	H ₃ CCH₂-	1	2	0	R	Н	•
1292	н ₃ с-СН ₂ -	1	2	0	R,	H	-CH ₂ -N-C
1293	Н₃С-СН₂-	1	2	0,	R .	н.	-сн ₂ -ү-с
1294	H₃C€	1	2	0	R	н	-CH ₂ -N-C-CF ₃
	H ₃ C-CH ₂ -					н	H
1296	H ₃ C-CH ₂ -	1	2	0	R	н	-cH₂-N-c-() scH₃
1297	H₃C-{	1	2	0	R	н	-CH ₂ -N-C-→0 F ₃ C
1298	H ₃ CO CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CH ₃ -CH ₂ -N-C-CH ₃ -CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃
					·		

Table 1.119

5	Compd.	R ² -(CH ₂) -	k	m	n	chirality	R³	-(CH ₂) - (CH ₂) - G-R ⁶
10	1299	H ₃ CO CH ₂ -	1	2	,	R	Н	-CH ₂ -N-C-CF ₃
	1300	OCH ₃	1	2	O	R	н .	-CH ₂ -N-C-CF ₃
15	1301	OCH ₃ H ₃ CO CH ₂ -	. 1	2	0	R	н	-CH₂-N-CCF3
20	1302	H ₃ CO CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
25	1303	H ₃ CO————————————————————————————————————	1	2	0	R .	, н	-CH ₂ -N-C-CF ₃
30	1304	H-CQ CH2-CH2-	1	2	0	R	н	-CH ₂ -N-C-CF ₃
35	1305	H ₃ CO-CH ₂ -	1	2	0	R	н '	-CH ₂ -N-C-CF ₃
	1306	H ₃ CCH ₂ Q H ₃ CO————————————————————————————————————					H	-CH ₂ -N-C-CF ₃
40	1307	H ₃ CO CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
45	1308	CH ₂ -	1	2	Ö	R	Н	-CH2-N-C-
50	1309	H ₃ CO CH ₂ -	1	2	0	R	н.	-CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃

Table 1.120

Compd. No.	R ² (CH ₂),	k	m	n	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} G - R^6$
1310	H ₃ CQ HO————————————————————————————————————	1	2	0	R	н .	-CH ₂ -N-C-CF ₃
1311	° CH₂-	1	2	0	R	н	-CH ₂ -N-C-CF ₃
1312	CH ₂ -	1	2	0	R .	н	-сн₂-ү-с-(СFэ
1313	Br CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
1314	O ₂ N CH ₂ -	1	2	0	R	н	-СH ₂ -N-С-СF ₃
1315	H ₃ C CH ₂ -	· 1	2	0	R · · · ·	· н	-CH ₂ -N-C-CF ₃
1316	F ₃ C CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
	O ₂ N CH ₂ -					н	-CH2-N-C-CF3
1318	с⊢С СН₂-	1	2	0	R	н	-CH2-N-C-CF3
1319	CH2−CH2−	1	2	0	R	Н .	-CH ₂ -N-C-CF ₃
1320	Br-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃

Table 1.121

5	Compd.	R ¹ (CH ₂) _j	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1321	CH	1	2	0	R	н	-CH2-NC-Br
15	1322	C├ ─ CH₂-	1	2	0	R	. н	-CH2-N-C
	1323	C├ - CH₂-	1	2	0	R	н	-CH2-N-C
20	1324	CH2-	1 ,	.2	0	R	H	-CH ₂ -N-C-CH ₃
25	1325	C├ - CH₂-	1	2	0	R ·	н.	-CH2-N-C
30	1326	CH-CH2-	• 1	2	. 0.	- R -	н -	-CH ₂ -N-C-
35	1327	C├ ─ CH ₂ -	1 .	2	0	R	н	-CH ₂ -N-C
40	1328	H ₃ C-CH ₂ -	1	2	0	R	н	-CH₂-N-C
45	1329	H ₃ C-CH ₂ -	1	2	0	R	н	-CH ² -N-C-CH ³
50	1330	. H₃C-{	1	2	.0	R	н	-CH2-N-C-CI
30	1331	H³C€H²-	1	2	0	R	н	-CH ₂ -N-C
55								

Table 1.122

5	Compd. No.	R ¹ /(CH ₂) _j	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1332	H ₃ C-CH ₂ -	1	2	0	R	н	-CH2-N-C
15	1333	H ₃ C-CH ₂ -	1	2	0	R	н	-CH₂-N-C
15		H ₃ C-CH ₂ -						-CH ₂ -N-C
20	1335	CH ₃ N CH ₂ - .CH ₃	1	2.	0	R .	н	-CH2-N-C-Spr
25	1336	CH ₃ CH ₂ - CH ₃	1	. 2	0	R	. н	сн₂-N-с-(СI -сн₃
30	1337	CH₃ N CH₂-	1,	2	0	<u>,</u> R	н .	-CH ₂ -N-C- H
35		CH ₃ N CH ₂ − CH ₃				•	н	-CH ₂ -N-C-→ HO
40		CH ₃ N—CH ₂ - CH ₃						-CH ₂ -N-C
45	1340	CH ₃ N CH ₂ - CH ₃	. 1	2	0	R	н	-CH ₂ -N-C
50	1341	CH ₃ N CH ₂ - CH ₃	1	2	0	R	н	-CH ₂ -N-C
		С⊢СН₂−						-CH2-N-C-CI
55					:			

Table 1.123

Compd. No.	R ² (CH ₂) _j	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶ R ⁵
1343	C⊢()−CH ₂ −	2	2	1	•	н	-сн ₂ - h-с- В сі сі
1344	с⊢СН₂-	2	2	1	-	н.,	-CH ₂ -N-C
1345	CH2−	2	2	. 1	-	н	-cH₂-N-C- HO CH₃
1346	CH2-	2	2	1	-	н	-cH ₂ -N-C-
1347	CH2-	1 [.]	2	0	R	н	-сн ₂ -N-С-(s) сн ₃
1348	H3C-CH2-					н	-сн ₂ -үс-үз
1349	CH ₃ CH ₂ -	1	Ż	0	R	н	-CH2-HC-STCH3
1350	С├-СН₂-		2	1	-	н	-CH2-N-C-STCH3
1351	с⊢(Сн₂-	1	2	0	R	н	-012-12 C-012
1352	H ₃ CCH ₂ -	1	2	0	R .	Н	-012-H C-013
1353	CH₃ CH₃	1	2	0	R	н	-013-H g-013

Table 1.124

5	Compd. No.	R2 (CH2);-	k	m	n	chirality	R³	$-(CH_2)_{p}$ $+\frac{R^4}{R^5}$ $(CH_2)_{q}$ $-\frac{1}{R^6}$
10	1354	C⊢√CH₂-	2	2	1 .	-	н	-013-H2-013
15	1355	CH2-CH2-	1	2	0	R	н	-CH ₂ -N-C-CN
	1356	H ₃ C-(-)-CH ₂ -	1	2	0	['] R	н	-CH ₂ -N-C-CN
20	1357.	CH ₃ N CH ₂ - CH ₃	1	2	0	R	н	-CH ₂ -N-C-CN
25	1358	с⊢{_}-сн₂	2	2	1	-	н	-CH ₂ -N-C-CN
30	1359	CH ₃ CH ₂ - CH ₃	. 1	2	0	R	н -	-CH²-H-C-
35	1360	CH ₃ CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
40	•	H ₃ CCH ₂ -						-сн₂-н-с
45	1362	CH ₃ CH ₂ - CH ₃	1	2	0	R	· н	-CH ₂ -N-C-CH ₃
	1363	CH ₃ CH ₂ -	1	2	0	R	н	-сн ₂ - N-с- Сн ₃
50	1364	H3C-CH2-	1	2	0	R	Ĥ	-CH ₂ -N-C
55								

Table 1.125

5	Compd. No.	R ¹ (CH ₂),	k	m	n	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} G - R^6$
10	1365	CH ₃ CH ₃	1	2	0	R	н	-CH ₂ -N-C
15	1366	CH₃ N CH₂- CH₃	1	2	0	R	н	-сн ₂ -N-с
	1367	н₃С-{СН₂-	1	2	0	R	н	-сн ₂ -N-с- Н
20	1368	CH-CH2-	1	2	0	R	н	-CH ₂ -N-C
25	1369	CH-CH ₂ -	1.	2	.0	R	н	-CH ₂ -N-C
30								-CH ₂ -N-C-SBr
35	1371	CH-CH2-	1	2	0	R	Н	-CH ₂ -N-C-
40	1372	CH-(-)-CH2-	1	2	0	R ·	Н	-01 ⁵ -H ₀ -
·	1373	H ₃ C⟨□}-CH ₂ -	1	2	. 0	R	н	-CH ₂ -N-C
45	1374	H ₃ C-CH ₂ -	1	2	0	R	н	CF ₃ -CH ₂ -N-C
50								-CH2-N-C-SBr
55								

Table 1.126

5	Compd.	R (CH ₂)	k	m	n	chirality	R³	$-(CH_2)_{p}$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
10	1376	H ₃ CCH ₂ -	1	2	0	R	Н .	-CH ₂ -N-C-
15	1377	н₃с-{сн₂-	1	2	0	R	Н	-cH2-N-C-
	1378	CH₃ N CH₂- CH₃	1	2	0	R	н	-CH2-N-C
20	1379	CH ₃ CH ₂ - CH ₃	1	2	0	R	Н	-CH ₂ -N-C
25	1380	CH ₃ CH ₂ - ·	1	2 .	0	R	н	-CH ₂ -N-C-S
30	1381	CH ₃ CH ₂ - CH ₃	1	2	0	<u> </u>	н	-CH ₂ -N-C-
35	1382	CH ₃ CH ₂ - CH ₃	1	2	0	R	н	-012-H-C-
40	1383	С⊢СН₂-	2	2	1	-	H .	-CH ₂ -N-C-CF ₃
45	1384	CH2-	2	2	1	- ,	Н .	-CH₂-N-C-\S Br
		C⊢————————————————————————————————————				-	н	-CH ₂ -N-C-
50	1386	CH2-	2	. 2	1	-	н	-012-HC-
55								- н

Table 1.127

5	Compd.	R ¹ / _P -(CH ₂) _j -	k	m	n	chirality	Ŕ³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10		CH ₃ CH ₂ − CH ₃					н	-CH2-N-C
15	1388	CH ₃ CH ₂ - CH ₃	1	2	0	R	н	-CH ₂ -H-C-(CH ₃) ₃ CH ₃
	1389	CH₃ N—CH₂- CH₃	1	2	0	R	н	-CH2-NC-\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\
20	1390	H ₃ C CH ₃ H ₃ C CH ₃	1	2	0	R	н	-CH ₂ -N-C-CF ₃
25	1391	H ₃ C — CH ₂ -	1	2	0	. R	н	-CH ₂ -N-C-CF ₃
30	1392	CI H ₃ C−CH ₂ −	1	2	0.	R	н	-CH ₂ -N-C-CF ₃
35	1393	н₃ссн ₂ —Сн ₂ -	1	2	0	R	н	-CH2-N-C-CF3
40	1394	O ₂ N H ₃ C-CH ₂ -	1	2	0	 R	н .	-CH ₂ -N-C-CF ₃
45	1395	H ₂ C=CH-CH ₂ -	1	2	0	Ŗ	н	-CH₂-N-C- CF₃
		H ₃ C-CH₂-					Н	-сн ₂ -N-с-С _Б
50	1397	Br CH ₂ -	1	2	0	R	Н	-CH ₂ -N-C-CF ₃
55								

Table 1.128

5	Compd.	R ¹ (CH ₂);-	k	m	n	chirality	. Ba	-(CH ₂) p G (CH ₂) q G-R⁶
10	1398	сн-сн-	1	2	0	R	н	-CH ₂ -N-C-CF ₃
	1399	CH- CH- CH-	1	2	0	; R	н	-CH2-N-C
15		CH-CH-	-				н .	-CH₂-N-C CF3
20	1401	H ₃ C-CH ₂ -	1	2 ·	0	R	н	-CH ₂ -N-C-N-CI
25	1402	H ₃ C-CH ₂ -	1	2	0	Ŗ	н	-CH ₂ -N-C
30	1403	H ₃ C-CH ₂ -	1	2	0	R	н .	-CH2-N-C-√N
35	1404	H ₃ CCH ₂ -	1	2	0	R	н	-CH2-N-C-
40	1405	H3C-{	1	2	0	R .	н	-CH2-N-C
	1406	H₃C-⟨CH₂-	1	2	Ö	R·	н	-сн ₂ -N-с-√сн ₃
45	1407	H ₃ C-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-N H ₃ CCH ₂ S
50	1408	H ₃ C-CH ₂ -	1	2	0	R	н	-CH2-N-C-N
55								

Table 1.129

5	Compd.	R ¹ (CH ₂) _j	k	m	n	chirality	[.] R³	-(CH ₂) p G (CH ₂) q G-R ⁶
10	1409	H ₃ C-CH ₂ -	. 1	2	0	R	н	-CH ₂ -N-C-CH ₃
15	1410	CH ₃ CH ₂ -	1	2	0	R	н	-CH2-N-C-
	1411	C	1	2	0	R	н	-CH2-N-C
20	1412	H ₃ C-CH ₂ -	1	2	0	R .	н	-CH2-N-C-C-NH
25	.1413	CH₃ CH₂-	· 1	2	0	R .	, н	-cH₂-N+C-C-NH
30	1414	Ci—CH₂-	2	2	1	-	н '	H2C-C-NH
35	1415	C├ - CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-SCN H ₂ N
40		H ₃ C-\(\bigc\)-CH ₂ -			O :	R	Н	-CH ₂ -N-C-SCN
45	1417	CH ₃	1	2	0	R	н	-CH ₂ -N-C-SCN H ₂ N
50	1418	C+-{-}-CH₂-	2	2	1	-	н	H ₂ N CH ₂ N-C H ₂ N
	1419	CH_CH2-	1	2	0	R	н	-CH ₂ -N-C-SH H H ₂ N
55						 		

Table 1.130

Compd.	R ² (CH ₂);	k	m	n	chirality	R³	$-(CH_2)_{p}$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
1420	H ₃ C-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-SH
1421	CH ₃ CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-SH
1422	с⊢СН₂-	2	2	1	-	н	-CH ₂ -N-C-SH H H ₂ N
1423	C├ - CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-
1424	H ₃ C-\CH ₂ -	1	2	0	R	.н	-CH ₂ -N-C
1425	CH ₃ CH ₂ −	·1	2	0	R	, _. н	-CH2-N-C
1426	СН2−СН2−	2	2	1	-	н	-CH ₂ -N-C-
1427	C├ - CH ₂ -	2	2	1	-	н	-CH ₂ -N-C-SH H H ₃ C-NH
1428	с⊷С}-сн₂-	2	2	1	-	н	-CH ₂ -N-C
1429	HCCH 20-CH2-	2	2	1	-	н	-CH2-N-C-
	CH ₂ -					н	-CH ₂ -N-C

Table 1.131

5	Compd No.	· R ¹ (CH ₂) _j	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1431	њссн ₂ о-{}-сн ₂ -	2	2	1	•	н	-CH ₂ -N-C
15	1432	O-CH₂-	2	2	1	-	н	-CH ₂ -N-C
	1433	нъсси20—СН2-	2	2	1	-	н	-сн _{х-М} с-х ни сн _х -хсн _х снь
20	1434	H2CCH2O-CH2-	2	2	1	-	· H	-CHT-NG-WHICH
25	1435	н₃ссн₂-Сн₂-	2	2	1	-	н .	-CH ₂ -N-C
30	1436	(HGC)2CH-CH2	2	2	1	<u>.</u> 	.	-CH ₂ -N-C-
35	1437	н ,с(сн ₂) ₂ о	2	2	1	-	н	-CH ₂ -N-C
40	1438	н₃ссн₂—Сн₂-	2	2	1	-	н	-CH ₂ -N-C
45	1439	(HG)2CH - OH7	2	2	1	•	H.	-CH ₂ -N-C
50	1440	Ӊ С(СН ₂)2О—(СН ₂	2	2	1		н .	-CH2-N-C-S
55	1441	H ₃ CS-CH ₂ -	2	2	1	. -	н	-CH2-N-C
33		·			 .			

Table 1.132

5	Compd. No.	R ¹ (CH ₂) _j	k	m	n	chirality	R³	$-(CH_2)_p + (CH_2)_q - G - R^6$
10	1442	ң ссн₂—С	l ₂ - 2	2	1	-	Н	-cH2-HC-CH2CH
15	1443	(њс)₂сн-С}-сн	r 2	2	1	-	н .	-CH2-N-C
	1444	н ₅ с(сн ₃)₂О-{	l ₂ - 2	2	1	:	н	-CH2-NCO(OH2) 3-CH6
20	1445	н₃ссн₂————сн	r 2	2	1	-	Н	-CH ₂ -N-C-H ₂ CH ₂ -CH ₂ CH ₃
25	1446	(HgC)2;CH-√CH	r 2	2	1	-	Н	-CH2-N-C
30	1447	ӊс(СН ₂) ₂ О(СН	₂ - 2	. 2	1		н	-012-N-C-1
35	1448	н₃сѕ-{-}-сн₂	- 2	2	i	-	н .	-CH2-N-C
40	1449	ңссн₂-√С-сң	₂ - 2	2	1	-	н	-CH ₂ -N-C-CF ₃
45	1450	(HgC)2CH-(-)-CH	r 2	2	1	• •	н	-CH ₂ -N-C
50	1451	(H ₃ CCH ₂) ₂ N	₂ - 2	2	1		н	-CH ₂ -N-C
	1452	но Н₃со—СҺ ₂	_ 2	2	1	•	н	-CH ₂ -N-C-CF ₃
55								

Table 1.133

5	Compd. No.	R ¹ (CH ₂) _j	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1453	н,с(сн ₂)₂О— Он ₂ -	2	2	1	-	н	-CH ₂ -N-C-CF ₃
15	1454	њсан 20 - €}-сн ₂ -	2	2	1	-	н	-CH ₂ -N-C-CF ₃
	1455	H₃CQ HO—CH₂-	2	2	1	-	н	-CH₂-N-C-CF3
20	1456	O-CH₂-	2	2	1	-	н	-CH₂-N-C-CF3
25	1457	(CH ₃) ₂ N-(CH ₂ -	2	2	1	-	н	-CH ₂ -N-C-
30	1458	H ₃ CQ HO—CH ₂ -	2	, 2	1	, -	, Н	$-CH_2-NC \longrightarrow H_2N$
35	1459	(H ₃ C) ₂ N-CH ₂ -	2	2	1	•	н	$-CH_2-N-C-\longrightarrow_{H_2N}^{P_1}$
40	1460	H ₃ CQ HO————————————————————————————————————	2	2	1	-	H	$-CH_2-N-C-$ H_2N H_2N
45		H0-CH2-					н	-CH2-NC-OH
	1462	H ₃ CQ HOCH ₂ -	2	2	1	-	н	-CH2-NC-ACH
50	1463	CH-CH2-	2	1	1	-	н	-сн ₂ -м-с-
55								

Table 1.134

5	Compd.	R ¹ (CH ₂)j-	k	m	n	chirality	R³	-(CH ₂) p (CH ₂) q G-R ⁶
10	1464	CH2-	2	1	1	-	н	-CH ₂ -N-C
15	1465	CH2-	2	1	1	-	Н	-CH ₂ -N-C
·	1466	с⊢СН₂−	2	1	1	· .	Н	-CH2-N-C-
20	1467	C⊢—CH₂-	2	1	1	-	н	-CH ₂ -N-C
25	1468	C├ - CH ₂	2	1	1	- .	н	-CH ₂ -N-C-\(\sigma\)
30	1469	CI—(¯)—CH₂-	2	1	1		н	-CH₂-N-C-CF3
35	1.470	CHCH ₂ -	2	1	1		н	-CH2-N-C-CI
40		CH2-				-	н	-CH2-N-CF
45	1472	CH ₂ -CH ₂ -	1	2	0	R	Н	P CF₃ -CH₂-N-C-
50	1473	CH ₃ CH ₂ - S CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃
	1474	CH ₃	1	2	0	R	н	-CH ₂ -N-C-CF ₃
55								

Table 1.135

;	Compd.	R ¹ (CH ₂) _j	k	m	n	chirality	R³	-(CH ₂) _p (CH ₂) _q G-R ⁶
0	1475	CH G CHF	1	2	0	R	н	-CH ₂ -N-C
5	1476	Br S CH₂-	1	2	0	Я	н .	-CH2-N-C-CF3
	1477	Br CH2-CH2	1	2	0	R	н	-CH2-N-C-CF3
0	1478	Br ()-012-	1	2	0	R	, н	-CH ₂ -N-C-CF ₃
5	1479	H ₃ C-CH ₃ CH ₃	1 .	2	0	R _.	н	-CH ₂ -N-C-CF ₃
o	1480	CH ₃ — CH ₂ -	1	2	- 0	R	· - н	-CH ₂ -N-C-CF ₃
5	1481	CH ₃ H ₃ C ← CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
0	1482	Br S−CH₂-	1	2	0	R	н .	-CH ₂ -N-C-CF ₃
	1483	H ₃ C CH ₂ -	1	2 .	0	R	н	-CH ₂ -N-C-CF ₃
5	1484	CF STS-CH ₂ -	.1	2	0	R	н	-CH ₂ -N-C-CF ₃
)	1485	H ₃ C-€ CH ₂ -	1	2	0	R	н	-CH₂-N-C-S

Table 1.136

5	Compd. No.	R ¹ (CH ₂),	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1486	H ₃ CCH ₂ -	1	2	0	R	. н	-CH ₂ -N-C
15	1487	н₃С-{_}СН₂-	1	2	0	А	н	-CH ₂ -N-C-
	1488	н₃С-{СН₂-	1	2	0	R	н	-cH₂-N-C-√
20	1489	H₃C-€	1	2	0	R	н	-сн₂-ү-с ◇
25	1490	н₃с-{	1	2 .	0	R	н	-CH₂-N-C-CH₃
30	1491 .	H ₂ C;—()—CH ₂	1.	,2	0	R.	н	-CH ₂ -N-C-\
35	1492	Н₃С-{СН₂-	1	2	0	R	Н	-CH ₂ -N-C-\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\
40	1493	CH ₃ CH ₂ - CH ₃	1	2	0	R	н	-o1-Hc-b
45								-CH₂-N-C
	1495	CH ₃	1	2	0	R	н	-CH ₂ -N-CN-CH ₃ H ₃ C
50	1496	CH ₃	1	2	0	R	Н	-CH ₂ -N-C-CH ₃ -CH ₂ -N-C-CH ₃ H ₃ C
55			·	·				

Table 1.137

5	Compd.	R ¹ (CH ₂),-	k	m	n	chirality	R ³	-(CH ₂) p (CH ₂) q G-R ⁶
10	1497	CH₃ N CH₂- CH₃					Н	-CH ₂ -N-C
15	1498	CH₃ N CH₂- CH₃	1	2	0	R	H ·	-CH2-N-C-✓
	1499	CH ₃ CH ₂ -	1	2	0	R	н	-CH₂-N-C✓
20	1500	CH ₃ CH ₂ - CH ₃	1	2	0	R	H-	-ċH⁵-Ы-Ç\CH3
25	1501	CH ₃ CH ₂ - CH ₃	1	2		. Я	н	-CH ₂ -N-C-
30	1502 ⁻	CH ₃ CH ₂ CH ₃	1	2 [.]	0	R	н	-CH ₂ -N-C
35	1503	CH ₃ CH ₂ - CH ₃	1	2	0	R	н	-CH2-NC-OCHF2
40	1504	H ₂ N-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
45	1505	CH ₂ O - CH ₂ -	1	2	0	R	н	-CH₂-N-C-
50	1506	CH2-	2	1	1	•	н	-CH ₂ -N-C
	1507	CH-CH2-	2	1	1	-	н	-CH ₂ -N-C
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Table 1.138

5	Compd. No.	R ¹ (CH ₂)	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1508	C	2	1	1	-	н	-CH ₂ -N-C
15	1509	CH-CH2-	2	1	1	-	н	-OH 5- H C-
15	1510	CH-{-}-CH2-	2	1	1	-	н	-CH ₂ -N-C-
20 -	1511	CH-CH ₂ -	2	. 1	1	-	н	-CH2-NC-S Br
25	1512	CH_CH2-	2	1	1		н	-CH2-N-C-
30	1513	CH2	.2	1,	.1	-	н	-CH2-N-C-
35	1514	(H ₃ CCH ₂) ₂ N	2	2	1	-	н	-CH2-N-C-
40	1515	HQ H ₃ CO—CH ₂ -	2	2	1	-	H,	-CH2-NC-CI
45	1516	(H ₃ CCH ₃) ₂ N-\-\-\-\-\-\-\-\-\-\-\-\-\-\-\-\-\-\-\	2	2	1	•	н	-CH ₂ -N-C
		HQ . H₃CO-CH₂-					н	$\begin{array}{c} H_2N \\ O \\ -CH_2-N-C \\ H_2N \\ \end{array}$
<i>50</i>	1518	HQ H₃CO————————————————————————————————————	2	2	1	•	н	-cH2-NCOH
55								-

Table 1.139

5	Compd. No.	R ² (CH ₂)	k	m	n	chirality	H3	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1519	HQ H ₃ CO—CH ₂ -	2	2	1		H.	-CH2-NCOCH
15	1520	вг—СН₂-	1	2	0	R	н	-CH2-N-C-
•	1521	н₃со-{Сн₂-	1	2	0	R	н	-CH ₂ -N-C-
20	1522	CH2-	1	2	0	R	н	-CH ₂ -N-C-S
25	. 1523	H₃CQ H₃CO————————————————————————————————————	1	2	0	R,	н	-CH2-N-C-S
30	1524	H ₃ CQ HO—CH ₂ -	1	2	0	R.	Н	-сн ₂ -N-с-
35	1525	Br—⟨CH₂-	1	2	0	R	н .	-CH₂-N-C-
40	1526	H ₃ CO-CH ₂ -	1	2	0	R ,	H	-CH ₂ -N-C
45	1527	H ₃ CQ H ₃ CO————————————————————————————————————	1	2	0	R	н	-CH₂-N-C-
	1528	H ₃ CQ H ₃ CO————————————————————————————————————	1	2		R.	н	-CH ₂ -N-C-OCF ₃
50	1529	H ₂ CQ HO-CH ₂ -	1	2	0	R	Н	-CH ₂ -N-C-OCF ₃
55								

Table 1.140

Con	npd. o.	R ²	CH ₂);—	k	m	n	chirality	. H3	-(CH ₂) _p + (CH ₂) _q G-R ⁶
153	0	B	CH2-	1	2	0	R	н	-CH2-N-C-(CF3
153	1	н₃со-{		1	2	0	R	н	-CH2-N-C-(CF3
153	2		}–сн₂–	1	2.	0	R	н	-CH2-N-C-(F3
153	3	H₃CO-{		1	2	0.	R	н	-CH2-N-C-CF3
153	4	H₃CQ HO—	_у_сн₂-	1	2	0	R	, н _{.:}	-CH ₂ -N-C
153	5	Вг)CH₂	.1	2.	.0	, R	. н	-CH ₂ -N-C
153	6	н₃со-{		1	2	0	R	н	-CH ₂ -N-C
153	7) CH ₂ -	1	2	0	R	н .	-CH₂-N-C-(CF3
153	8	н₃со н₃со-{		1	2	0	R	н	-CH ₂ -N-C
153	9	H ₃ CQ	CH₂-	1	2	. 0	R	н	-CH ₂ -N-C
154	0	Вг	CH2-	1	2	0	R	н	-CH ₂ -N-C-\-F
			·		· · · · · · · · · · · · · · · · · · ·		· .		

Table 1.141

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5	Compd.	R ² (CH ₂),	k	m	n	chirality	R³	$-(CH_2)_{p} + \frac{R^4}{R^5} (CH_2)_{q} - G - R^6$
10	1541	H ₃ CO-CH ₂ -	1	2.	0	R	н	-CH ₂ -N-C-F
	1542	CH ₂ -	1	2	0	. R	н	-CH ₂ -N-C
15	1543	H ₃ CO C C H ₂	1	2	0	R	н	-CH2-N-C
20	1544	H ₃ CQ HO————————————————————————————————————	.1	2	0	R	н	-CH2-H-C-CF3
25	1545	CL_S_CH₂-	1	2	. 0	R	н.	-CH2-N-C-CF3
30	1546	H ₃ CO F CH ₂ -	1	2	0	R	H	-CH ₂ -N-C-CF₃
35	1547	H ₃ CO—Br	1	2	0	R	, H	-CH ₂ -N-C CF₃
40	1548	H ₃ C-CH ₂ -	1	2	0	R	Н	-CH ₂ -N-C
	1549	H ₃ C-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
45	1550	н₃с-{Сн₂-	1	2 .	0	R	н	-012-HV-C-N-C-OCH,
50	1551	н₃с-{	1	2	0	R	H	-сн2-4 с-

Table 1.142

	Compd.	R ¹ (CH ₂) _j -	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
)	1552	H ₃ C-\(\bigcap\)-CH ₂ -	1	2	0	R	н	-CH2-N-C-
5	1553	H₃C-(1	2	0	R	Н	-012-Hc-65
•	1554	н₃С-{СН₂-	1	2	0	R	н	-CH2-N-C
•	1555	H ₃ C-CH ₂ -	1	2	0	R	н	-CH2-N-CH3 N H3C
5	1556	н₃с-{	1	2	0	R	н	
)	1557	н₃с-{	1	2	0	R	н	-CH2-N-C-N H3C
	1558	H ₃ C-CH ₂ -	1	2 .	0	R	н .	-CH ₂ -N-C-N-CH ₃
		H ₃ C-⟨CH ₂ -					н	-CH ₂ -N-C-(CH ₃) ₃
	1560	H₃C-(CH₂-	1	2	0	R	Н	-CH ⁵ -M-C-√-M
	1561	H ₃ C-(1	2	0	R	н	$-CH_{2}-NC$ $-CH_{3}$ $-CH_{3}$ $-CH_{3}$ $-CH_{3}$
	1562	H ₃ C-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C

Table 1.143

Compd.	R ¹ (CH ₂) _j -	k	m	n	chirality	· R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
1563	H ₃ C-()-CH ₂ -	1	2	0	R	Н	-cH'-HC
1564	H₃C-⟨CH₂-	1	2	0	R	н	-012-Hz-
1565	CH ₃ CH ₂ - CH ₃	1	2	0	R	н	-CH ₂ -N-C
1566	CH ₃ CH ₂ − CH ₃	1	2	0	R	н	-CH ₂ -N-C
1567	CH³ CH³-				R	Ĥ	-01,-Ho-
1568	CH ₃ CH ₂ -				R	н	-01-12c-
1569	CH ₃ CH ₂ - CH ₃	1	2	0	R	н	-сн М. с. — М. :
1570	H ₃ CS-CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
1571	н₃сѕ-{_}-сн₂-	2	2	1	-	H	-CHZ-NC-SCH
	Cho Cons					н	-CH ₂ -N-C-CF ₃
1573	H,CO	2	2	1	-	н	-CH ₂ -N-C-CF ₃

Table 1.144

5	Compd.	R ¹ (CH ₂)	k	m	n	chirality	[^] R ³	$-(CH_2)_{p} + (CH_2)_{q} - (CH_2)_{p} + (CH_2)_{q} - (CH_2)_{q}$
. 10	1574	μο-Ο-μ°	2	2	1	-	н	-CH ₂ -N-C-CF ₃
15	1575	с	2	2	, 1	-	н	-CH ₂ -N-C-CF ₃
,,	1576	€_MC-{	2	2	1	-	· н	-CH ₂ -N-C-CF ₃
20	1577	HOICHT THE CHT	2	2	1	-	H	-CH2-N-C
25	1578	н,с Н с — сн ₂ -	2	2	1		н	-CH ₂ -N-C-CF ₃
30	1579	Q-1, c-Q-cH³-	2	2	1	-	н	-сн ₂ -N-с-СF ₃
35	1580	→ μ°c → C+3-	2	2	1	-	н	-CH ₂ -N-C-CF ₃
	1581	Ci—CH ₂ -	2	2	1	-	н	-CH2-NC
45	1582	CH2-	2	2	1	-	н	-01-H-C-4-3
	1583	CH_CH2-	1	2	0	R	н	-CH ₂ -N-C
50	1584	с⊢{	. 1	2	0	R	н	$-CH_{2}-N\cdot C$ $+U_{2}N$ $+U_{2}N$ $-CH_{2}-N\cdot C$ $+U_{2}N$ $+U_{2}N$
55								

Table 1.145

5	Compd.	R ¹ (CH ₂),	k	m	n	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} - G-R^6$
10	1585	C⊢—Ç—CH₂-	1	2	0	R	~ Н	-CH2-N-C-S
15	1586	C├ - CH₂-	. 1	2	0	R	. H	-CH2-N-C-\CI
	1587	C├ - CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-
20	1588	с 	1	2	0	R	н	-CH₂-N-C-
25	1589	H ₃ C-CH ₂ -	.1	2	0	R	, H	-CH ₂ -N-C-CF ₃
30	. 1590	H ₃ C-CH ₂ -	1	2	0	<u>"R</u>	, Н .	-CH ₂ -N-C
35	1591	H ₃ C-CH ₂ -	1	2	0	R	·H	-CH ₂ -N-C-Br
40		H ₃ C-CH ₂ -					н	-CH ₂ -N-C-\square
45	1593	H ₃ C-CH ₂ -	1	2	0	R	н	-CH2-N-C-
50	1594	CH ₃ N CH ₂ - CH ₃	1	2	0	R	н	-CH ₂ -N-C
	1595	CH ₃ CH ₃	1	2	0	R	н	-CH ₂ -N-C
55							<u>.</u>	

Table 1.146

5	Compd. No.	R ¹ (CH ₂)	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q -G-R ⁶
10	1596	CH3 CH3	1	2	0	R	н	-CH ₂ -N-CN
15	1597	CH₃ CH₃-	1	2	0	R	. н .	-CH2-MC-\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\
		CH ₃ N CH ₂ -					Н	-CH ₂ -N-C-
20	1599	CH₃ N CH₂- CH₃	1	2	0	R	н	-CH ₂ -N-C-CH ₃
25	1 600	C├ ~ CH₂-	2	. 2	1	-	н	-CH ₂ -N-C-CF ₃
30	1601	CH2-		•			н	-CH ₂ -N-C
35	1602	с⊢—СН₂-	2	2	1	-	н	-CH ₂ -N-C-
40	1603	C⊢————————————————————————————————————			1	•	н .	-CH2-N-C-
45	1604	C⊢Ç,-CH₂-	2	2	1	-	н	-CH ₂ -N-C-
	1605	CH2-	2	2	1	-	н	-CH ₂ -N-CCH ₃
50	1606	C├ - CH ₂ -	1	2	0	R	H	-CH ₂ -N-C
55								•

Table 1.147

5 .	Compd.	R ¹ (CH ₂),	k	m	n	chirality	H3	$-(CH_2)_{p} + (CH_2)_{q} G - R^5$
		H ₃ C-{CH ₂ -					н	P SCF ₃
10		CH₃ N CH₂-					н	-CH ₂ -N-C
15		CH₃ CH₂-						205
20					•	•	H	-CH ₂ -N-C
25		CE, b CH2-CH2-				-	н	-CH2-N-C
	1611	CH-CH-CH-	2	2	. 1	-	н	-CH₂-N-C CF3
30							н	-CH₂-N-C-CF3
35	1613	, c-(C)	2	2	1	-	н	-сн ₂ -N-с-С-Б
40	1614	F ₃ CS—CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
<i>45</i>	1615	F3CS-{\bigce}-CH2-	2	2	1	-	н	-CH ₂ -N-C-CF ₃
43	1616	F3CS-CH2-	2	2	1		Н	-CH ₂ -N-C- -CH ₂ -N-C- H ₂ N
50	1617	F3C5-(CH2-	2	2	1	-	н	-CH ² -N-C- BL
55								11214

Table 1.148

5	Compd.	R ² (CH ₂)j-	k	m	n	chirality	R ³	$-(CH_2)_{\overline{p}} + (CH_2)_{\overline{q}} - G - R^6$
10	1618	HQ H ₃ CO—CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-
15	1619	но н ₃ со—Сн ₂ -	1	2	0	R .	н .	-CH₂-N-C-COCF3
	1620	HQ H ₃ CO————————————————————————————————————	1	2	0	R	Н	-CH ₂ -N-C-CF ₃
20	1621	HQ H ₃ CO—CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
25	1622	H ₃ CO————————————————————————————————————	1	2	0	. R	н	-CH₂-N-C-CF₃
<i>30</i>	1623	но—СН₂-	1	2	,0,,	R	н	-CH ₂ -N-C-Br
35		но-СН-					H [°]	-CH ₂ -N-C
40		но-√сн₂-					н ·	'' - F
45	1626	но-{СН₂-	1	2	0	R	н	-CH ₂ -N-C
50	1627	HO-CH ₂ -	1	2	0	R	н	-CH ₂ -N-CF
,	1628	н₃сѕ-{Сн₂-	1	2	0	R	. н	-CH ₂ -N-C- H F
55								

Table 1.149

5	Compd.	R ² (CH ₂),	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1629	H₃CSCH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
15	1630	H ₃ C CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
	1631	H2NCH2-CH2-	1	2	0	R ·	н.	-CH ₂ -N-C-CF ₃
20	1632	CF ₃ -€N-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
	1633	H ₃ CS NC-CH ₂ -	1	2	0	R.	н .	-CH ₂ -N-C
30	1634	(њс)₂сн-СН₂г	, 1	.2	0	R	н	-CH ₂ -N-C-CF ₃
35	1635	H ₃ C-CH ₂ -	1	2	0	R	н	-CH ₂ -N-С-С(СН ₃) ₃
40	1636	H ₃ C-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C CH ₃
45	1637	CH ₃	1	2	0	R	· н	-OH2-N-C-(CH2)4CH3
50	1638	CH3 CH3	1	2	0	R	н	-CH2-N-C
30	1639	CH₃ O CH₂-	1	2	0	. R .	н .	-CH2-HC
55								

Table 1.150

5	Compd.	R ² (CH ₂)	 k	m	n	chirality	R³	$-(CH_2)_{p}$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
10	1640	CH₃ N CH₂- CH₃	1	2	0	R .	н	-CH2-M-C(CH2)3CH3
15	1641	CH₃ CH₂− CH₃	1	. 2	0	R	н	-CH2-N-C
	1642	CH ₃ CH ₂ CH ₃	1	2	. 0	R	, н	$-CH_2-N-C-N$ O_2N-N
20	1643	CH ₃	1	2	0	R [.]	н	-CH2-N-C-
25	1644	CH ₃ CH ₂ - CH ₃	1	2	0.	R	н	-CH ₂ -N-C
30	1645	CI CH₂-	1	2	0	R _. .	· н	-CH ₂ -N-C-CF ₃
35	1646	Br CH ₂ -	1	2	0	R	н	-CH2-N-C-CE3
40	1647	н₃с(сн₂)₃{Сн₂-	2	2	1		н	-CH ₂ -N-C-CF ₃
45	1648	H ₃ C(CH ₂) ₃ —()—CH ₂ -	1	2	0	R	H .	-CH ₂ -N-C-CF ₃
	1649	н ₃ С(СН ₂) ₂ —СН ₂ -	2	2	1	-	н	-CH₂-N-C-CF3
50	1650	H ₃ C(CH ₂) ₂ —CH ₂ -	1	2	0	R	н	-CH₂-N-C-CF3
55								

Table 1.151

5	Compd.	R ² (CH ₂) _j	k	m	ก	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10 .	1651	н,с(сн,),-Сн,-	2	2	1		н	-CH2-NC-
15	1652	H ₃ C(CH ₂) ₃ —CH ₂ -	2	2	1	-	н ·	-CH ₂ -N-C-Br
	1653	H ₃ C(CH ₂) ₂ -CH ₂ -	2	2	1	-	н	-CH2-NC+
20	1654	H ₃ C(CH ₂) ₂	2	2	1	-	н	-CH ₂ -N-C
25	1655 ,	H ₃ C(CH ₂) ₃ {-}-CH ₂ -	2	2	1	-	н,	-CH2-NC
30	1656	H ₃ C(CH ₂) ₃ -CH ₂ -	2	2	1	<u>-</u>	н ,	-CH ₂ -N-C
35	1657	H ₃ C(CH ₂) ₂	2	2	1	•	н	-cH2-NG-
40	1658	H ₃ C(CH ₂) ₂	2	2	1	-	Н	-CH ₂ -N-C-()
45	1659	CH-CH2-					н	-CH ₂ -N-C-
50	1660	ВСН₂-	1	2	0	R	н	-CH ₂ -N-C
	1661	Br—CH ₂ -	1	2	0	R	H .	$-CH_{2}-N-C$ $H_{2}N$ $-CH_{2}-N-C$ $H_{2}N$ $-CH_{2}-N-C$ $H_{2}N$
55								

Table 1.152

5	Compd. No.	R ² (CH ₂) _j	k	m	n	chirality	R³	$\frac{R^4}{CH_2_0}(CH_2_0^-G-R^6)$
10	1662	ВСН₂-	1	2	0	R	н	-CH ₂ -N-C
15	1663	Вг—СН ₂ -	1	2	0	R	н <u>́</u>	-CH ₂ -N-C
	1664	н₃сѕ-{сн₂-	2	2	1	-	н	-CH ₂ -N-C
20	1665	н₃сs——сн ₂ -	2	2	1	-	н .	-CH ₂ -N-C
25	1666	н₃сѕ-{сн₂-	2	2	1	-	н.	-CH ₂ -N-C-F H ₂ N
30	1667	H ₂ CCH ₂ -CH ₂ -	2	2	1		н	-CH₂-N-CBr
35	1668	н₃ссн ₂ —⟨¯)—сн ₂ -	2	2	1	· .	·н	-CH ₂ -N-C
40	1669	н₃ССН ₂ —{СН ₂ -	2	2	1	-	н	-CH ₂ -N-C
45	1670	H3CCH2-CH2-	2	2	1	-	н	-CH ₂ -N-C
50	1671	н₃ССН ₂ —⟨СН ₂ -	2	2	1	i	н	-CH ₂ -N-C
<i>3</i> 0	1672	H3CCH2-CH2-	2	. 2	1	-	н	$-CH_{2}-N-C$ $-CH_{2}-N-C$ $+1_{2}N$ $-CH_{2}-N-C$ $+1_{2}N$ $-CH_{2}-N-C$ $+1_{2}N$ $-CH_{3}-N-C$ $+1_{2}N$ $+1_{3}N$ $+1_{4}N$
55								

Table 1.153

5	Compd.	R ¹ (CH ₂) _j	k	m	n	chirality	. R3	$-(CH_2)_{p+1}^{R^4}(CH_2)_{q}G-R^6$
10	1673	H3CCH2-CH2-				-	н .	-CH2-N-C- Br C1
	1674	F(2	2	1	-	. н	-CH ₂ -N-C- Br
15	1675	├ ─ ○ CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
20	1676	F-CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
25	1677	F-CH ₂ -	2 .	2	1	-	н	-CH ₂ -N-C-Br
30	1678	F-CH ₂ -	2	2 .	1	-	н.	-CH ₂ -N-C
35	1679	F—CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
40	1680	F—CH₂-	2	2	1	-	н	-CH ₂ -N-C
45	1681							$-CH_2-N -C - $ H_2N
	1682	F——CH₂-	2	2	1	-	н	-CH ₂ -N-C
50	1683		2	2	1	-	H	-CH ₂ -N-C-OB ₁
55								

Table 1.154

Compd.	R ² (CH ₂);-	k	m	n	chirality	R³	$-(CH_2)_{\overline{q}}^{\overline{H}^4}$ $(CH_2)_{\overline{q}}^{\overline{q}}G-R^6$
1684	~ # c-<>- c+²-	2	2	1	-	н	-CH ₂ -N-C
1685		2	2	1	·	н	-CH ₂ -N-C
1686	C-HC-CH2-	2	2	1	-	н	-CH ₂ -N-C
1687	- N° c-√	2	2	1	-	, H	-CH ₂ -N-C
1688	○- 12°>c+2-	2	2	1		H	-CH ₂ -N-C
1689		2	2	1	-	H .	-CH ₂ -N-C
1690	O-14°-	2	2	1	-	н	-CH ₂ -N-C-CF ₃
1691		2	2	1	~	н	-CH₂-N-CS-CI
1692	CH ₃	1	2	0	R	H	-CH ₂ -N-C-OBr
1693	H ₃ C-CH ₃	1	2	0	R	н	-CH ₂ -N-C
1694	H ₃ C-CH ₂ -CH ₂ -	1	2	0	R	н .	H ₂ N -CH ₂ -N-C

Table 1.155

Compd. No.	R ² (CH ₂)	k	m	·n	chirality	· R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
1695	H ₃ C ← CH ₂ −	1	2	0	R	Н	-CH ₂ -N-C
1696	.СH ₃ Н ₃ С—СН ₂ -	1	2	0	R	н	-CH2-N-C
1697	CH ₃	1	2	0	R	н	-CH ₂ -N-C-CI
1698	CH ₃ CH ₂ -	1	2	0	R	н	$-CH_2-N-C-$ H_2N H_2N
1699	CH ₃	1	2	0	R	H	-CH ₂ -N-C
1700	CH ₃	1	2	0	R ·	н	-CH ₂ -N-C
1701	н ₂ С=СН—СН2−	1	2	0	R	н	-CH ₂ -N-C
	H ₃ CO————————————————————————————————————					н	-CH ₂ -N-C
1703	CH _z -	1,	2	0	R	H	-CH ₂ -N-C
1704	HO-CH ₂ -	1	2	0	R	H	-CH ₂ -N-C- H ₂ N
1705	CH_CH2-	1	2	0	R	н	$-CH_{2}-NC$ $-CH$

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5	Compd.	R ² (CH ₂)	k	m	n	chirality	. ^L 3	$-(CH_2)_{p} + (CH_2)_{q} G - R^6$
. 10	1706	CH₂-	1	2	0	R	н	-CH ₂ -N-C-CF ₃
	1707	H₃CS-()-CH ₂ -	1	2	0	R	H·	-CH ₂ -N-C H ₂ N
15	1708	н₃ссн₂—()—сн₂-	1	2	0	R	н	-CH ₂ -N-C
20	1709	(H ₂ C)2CH	. 1	2	.0	R	н	-CH ₂ -N-C- H ₂ N
25	1710	H ₃ C Br—CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
<i>30</i> ·	1711	CH ₃	1	2	0	R	. ⊎	-CH₂-N-C-
35	1712	HO-CH2-CH2-	1	2	0	R	. н	-сн ₂ -ү-с-⟨СF ₃
33	1713	H ₃ C HO—CH ₂ -	1	2	0	R	н	-сн - N-с
40	1714	HQ H ₃ CO————————————————————————————————————	1	2	0	R	Н	-сн₂-N-С-СF ₃
45	1715	N CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
50 .	1716	CH ₂ -	1	2	0	R	H	-CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃ -CH ₂ -N-C-CF ₃

Table 1.157

Compd.	R ¹ (CH ₂)	k	m	n	chirality	R³	$-(CH_2)_{\overline{p}} + (CH_2)_{\overline{q}} - G - R^6$
1717	H ₃ CO-⟨\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	1	2	0	R	н	-CH ₂ -N-C-CF ₃
1718	CH3 CH3	1	2	0	R	н	-CH ₂ -N-C-CF ₃
1719	£ 1/2 - CH ² -	1	2	0	R .	н	-CH ₂ -N-C-CF ₃
1720	ньсо-с ньсо-с - сн ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
1721	н ₃ ССН ₂ —СН ₂ -	1	2,	0	R	н	-CH ₂ -N-C- H
1722	CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
1723	-CH ₂ -	1	2	0	R	Н	-CH₂-N-C-CF3
1724	CH ₃	1	2	0	R	н	-CH ₂ -N-C-CF ₃
1725	CH ₃ -CH ₂ -	1	2	0	R	H	-CH ₂ -N-C
1727	CH₂-	1	2	0	R	н	-CH ₂ -N-C

Table 1.158

5	Compd. No.	R (CH ₂),-	k	m	n	chirality	R³	$-(CH_2)_{\overline{p}} + (CH_2)_{\overline{q}} G - R^6$
10	1728	-CH ₂ -	1	2	0	R	н	-CH₂-N-C-CF3
15	1729	CH ₃	1	2	0	R	н	-CH₂-N-C-CF3
	1730	H ₃ C C C C C C C C C C C C C C C C C C C	1	2	0	R	н	-CH ₂ -N-C
20	1731	H ₃ CCC N CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
25	. 1732	HOCH2-CH2-	1	2	0	R .	н	-сн ₂ -N-с-С-Б ₃
30	1733		1	2	0	R.	H	-CH ₂ -N-C- H F
35	1734	H₃CS—CH₂-	1	2	0	R	Н	-CH₂-N-CF
40		н ₃ ссн ₂ ————————————————————————————————————		2			H	-CH₂-N-CFF
45	1736	CH₂-	1	2	0	R	н	-CH ₂ -N-CF
	1727	CH ₃	1	2	0	R	н	-CH-N-C
50	1738	H ₃ C — CH ₂ -	1	2	0	R	н	H F F CF ₃ −CH ₂ −N-C−F F
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5	Compd.	R ² (CH ₂);	k	m	п	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1739	(H ₂ C) ₂ CH-()-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
15	1740	CH ₂ -	1	2	0	R	н	-CH₂-N-C-Br
	1741	H₃CS()-CH₂-	1	2	0	R	н	-CH₂-N-C-S
20	1742	н ₃ ссн ₂ ————сн ₂ -	1	2	0	R	н	-CH₂-N-C-
25	1743	CH₂-	1	2	0	R	• н	-CH ₂ -N-C-✓Sr
30		CH₃ H₃C—————————————————————————————————				•	H '	-CH ₂ -N-C-
35	1745	H ₃ C ← CH ₂ − CH ₂ −	1	2	0	R	н	-CH₂-N-C-
40	1746	(HGC)2CH CH2	1	2	0	R	н	-CH2-N-C-
45	1747	-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
		њссн₂—Сн₃-					н	-CH ₂ -N-C-Br
50	1749	CH ₃ ·	1	2	0	R	н	-CH2-N-C
55								

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5	Compd.	R ¹ (CH ₂),	k	m	n	chirality	R³	-(CH ₂) _{p 1} (CH ₂) _q G-R ⁶
10	1750	СН2-	1	ż	0	R	н	-CH ₂ -N-C-
15 .	1751	H₃CS€	1	2	0	·R	н	-CH ₂ -N-C-OCF ₃
20	1752	н ₃ ссн ₂ —Сн ₂ -	1	2	0	R .	Н	-сн ₂ -м-с-
,	1753	-CH ₂ -	1	2	0	R	н	-CH2-N-C-
25	1754	СН ₃	1	2	0	R	Н	-CH ₂ -N-C-C
30	1755	CH ₃ H ₃ C ← CH ₂ − H ₃ C	1	2	0	· R	н	-CH₂-N-C
35 [°]	1756	(4,0,0,0,0,0)	1	2	0	R	н	-CH2-N-C-C
40		Br Br CH ₂ -					Н	-CH ₂ -N-C-CF ₃
45	1758	H ₃ COBr CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
45	1759	н₃с-{	1	2	0	R	н	-01-mc
50	1760	H ₃ C-CH ₂ -	1	2	0	R	Н	CF ₃ -CH ₂ -N-C -OI-N-C OI-N-C OI-N-
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Table 1.161

	Compd.	R ¹ (CH ₂),	ما			ahiralitu	. Dj	$-(CH_2)_{p} + G^{4} + (CH_2)_{q} - G^{-R^6}$
5	No.	R ² (0112/j				Crimanty		R5
10	1761	H₃C-(CH₂-	1	2	0	R	н	-CH2-HC-CI
15	1762	CH₃ CH₂-	1	2	0	R	н	-CH ² -H, C-V
15	1763	CH2-	2	2	0	-	н	-CH ⁵ -N-C-OCH ⁵ CH ³
20	1764	СН₂-	2	2	0	-	н	-CH2CH2-N-C
25	1765		2	2	0	-	н	(S) OCH ₂ CH ₃ -CH-N-C-CH ₂ CH ₃ CH ₂ CH(CH ₃) ₂
30	1766	CH ₂	2	2	0	• •	Н	(A) OCH ₂ CH ₃ -CH-N-C
35	1767	CH2-	1	3	1	-	н	-CH ₂ -N-C-OCH ₂ CH ₃
40	1768	CH2-	1	3	1		н	-CH2CH2-N-C-
45								CH2 HCF2O
	1770	CH ₃	1	2	0	R	н	-c4-Hc-OHCO
50								-cH2-4-C- (H3C)3C-C++4-C H3C
55								

Table 1.162

5	Compd.	R ¹ (CH ₂) _j	k	m	n	chirality	R ^o	$-(CH_2)_{p} + (CH_2)_{q} - G - R^6$
10	1772	CH ₃ CH ₂ - CH ₃	1	2	0	R ·	н	-CHI-N-C
	1773	CH ₃ CH ₂ - CH ₃	1	2	0	R	н	H ₃ C - H C - H C O
15	1774	CH ₃ CH ₂ CH ₃	1	2	0	R	н	-CH ₂ -M-C-N-C-H ₃ -OCH ₃
20	1775	H0-CH ₂ -	1	2	0	R	Н	-CH ₂ -N-C
25	1776	H3 CO-CH2-	1	2	0	R	н	CH ₂ -N-C
30	1777	CH ₂ -CH ₂ -	2	2	1	• .	H .	-CH ₂ -N-C
35	1778	H₃C-{	2	2	1	-	H	-CH ₂ -N-C
40	1779	CH ₂	2	2	1	-	H	-CH ₂ -N-C-F ₃
45	1780	Br—CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
	1781	HO-CH ₂	2	2,	1	-	н	$-CH_{2}-N-C$ $H_{2}N$ $-CH_{2}-N-C$ $H_{2}N$ $H_{2}N$
50		H ₂ C=CH-(-)-CH ₂ -					н	-CH ₂ -N-C-CF ₃
55								_

Table 1.163

								4
5	Compd. No.	R ² (CH ₂) _j	k	m	n	chirality	. H3	$-(CH_2)_{p}$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
10	1783	NC-⟨CH ₂ -	2	2	1	٠	н	-CH ₂ -N-C
15	1784		2	2	1	•	. н	-CH ₂ -N-C-CF ₃
13	1785	CH ₃ (CH ₂) ₂	2	2	1		н	-CH ₂ -N-C-CF ₃
20	1786	- CH ₂ -	2	2	1	-	Н	$-CH_2-N$ H_2N CF_3
25	1787	сн ₃ (Сн ₂) ₂ —Сн ₂ —	· 1	2	0	R	Н	-CH ₂ -N-C
30	1788	H ₃ C—CH ₂ —CH ₂ —	2	2	1	· _	H	-CH ₂ -N-C
35	1789	H₃CO-{	2	2	1	-	н	-CH ₂ -N-C-CF ₃
40	1790	CH2-	1	2	0	S	H	-CH ₂ -N-C
45	1791	C	.1	2	0	S	н	-CH ₂ -N-C
	1792	CH ₃ H ₃ C————————————————————————————————————	. 2	2	1	-	Н	-CH ₂ -N-C
50	1793	CH ₂ -CH ₂ -	2	2	1	•	н	-CH ₂ -N-C
55								

Table 1.164

5 .	Compd.	R ¹ (CH ₂),-	k	m	n	chirality	. _{Ba}	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1794	H ₃ C-CH ₂ -	2	2	1	-	Н	-CH ₂ -N-C
	1795	CH₂-	2	2	1	-	н	-CH ₂ -N-C
15	1796	8CH2-	2	2	1	-	н	-CH ₂ -N-C
20	1797	HO(-)CH ₂ -	2	2	1	-	H .	-CH ₂ -N-C-F H ₂ N
25	1798	H ₃ CO-CH ₂ -	2	2	1	-	Н	-CH ₂ -N-C
30	1799	H ₂ C=CH-(2	2	1	-	н	-CH ₂ -N-C-F H ₂ N
35	1800	NC-CH₂-	2	2	1	-	н	-CH ₂ -N-C-F H ₂ N
40	1801	CH ₂ −	. 2	2	1	-	Н	-CH ₂ -N-C-F H ₂ N
45	1802	HO-CH ₂ -	1	2	0	R	н	-CH ₂ -N-CF ₃
	1803	HO-CH ₂ -	1	2	0	R	н	$-CH_{2}-N$ $-CH_{2}-N$ $-CH_{2}-N$ $-CH_{2}-N$ $-CH_{2}-N$ $-CH_{2}-N$ $-CH_{2}-N$ $-CH_{2}-N$ $-CH_{3}-N$ $-CH_{2}-N$ $-CH_{3}-N$ $-CH_{3}-N$ $-CH_{4}-N$
50		H3C(CH2)3-CH2-						-CH ₂ -N-C
55					 			

Table 1.165

5	Compd.	R (CH ₂)-	k	m	n	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} - (CH_2)_{q} - (CH_2)_{q} - (CH_2)_{q}$
10	1805	Br—CH ₂ -	1	. 2	0	R	H	-CH ₂ -N-C-SCF ₃
	1806	H ₃ CO-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-SCF ₃
15	1807	H ₃ CQ	1	2	0	R	Н	-CH ₂ -N-C
20	1808	HQ H ₃ CO—CH ₂ -		2	0	R	н	-CH ₂ -N-C-SCF ₃
25	1809	HOCH₂-	1	. 2	0	·R	н	-CH ₂ -N-C-SCF ₃
30	1810	CH2-	1	2	0	R	, H	-CH2-N-C-SCF3
35	1811	-CH ₂ -	1	2	0	R	Н	-CH2-N-C-SCF3
40	1812	H₃CS-CH₂-	1	2	0	R	Н	-CH ₂ -N-C-SCF ₃
	1813	н₃ссн₂-{}-сн₂-	1	2	0	R	н	O SCF ₃ .
45	1814	CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-SCF ₃
50	1815	CH ₃ H ₃ C-⟨ CH ₂ -	1	2	0	R	н	-CH2-N-C-SCF3
55						 -		

Table 1.166

5	Compd.	R ¹ (CH ₂)	k	m	n	chirality	. _{K3}	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1816	(CH ₃) ₂ C H	1	2	0	, R	н.	-CH ₂ -N-C-SCF ₃
	1817	(CH ₃) ₃ C	1	2	0	R	н	-CH ₂ -N-C-SCF ₃
15	1818	Br—CH ₂ -	1	2	0	R	н .	-CH ₂ -N-C-OCHF ₂
20	1819	H3CO-CH2-	1	2	0	R	н	-CH ₂ -N-C-C
25	1820	H ₃ CQ HO-СН ₂ -	1	2	0	R	н	-CH ₂ -N-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-C-
30	1821	HQ H₃CO-CH₂-	1	2	0	R	н	-CH ₂ -N-C-
35	1822	HO(CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-C
	1823	CH ₂ -	1	2	0	R	н .	-CH ₂ -N-C-OCHF ₂
40	1824	-CH ₂ -	1	2	0	R .	Н	-CH ₂ -N-C
45	1825	H3CS-CH2-	1	2	0	R	н	-CH ₂ -N-C-OCHF ₂
50	1826	H₃CCH₂CH₂-	1	2	0	R	н	-CH ₂ -N-C-OCHF ₂

Table 1.167

5	Compd.	R ¹ (CH ₂)j-		k	m	п	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} G - R^6$
10	1827	CH ₂ -		1	2	0	R	н	-CH ₂ -N-C
	1828	CH ₃	_	1	2	0	R	н	-CH ₂ -N-C-OCHF ₂
15	1829	H ₃ C CH ₂	-	1	2	0	R	н	-CH ₂ -N-C
20	1830	(СН₃)₂С Н- СН	17	1	2	0	R	н	-CH ₂ -N-C-
25	1831	Br—€ CH ₂ -		1	2	0	R.	н	-CH ₂ -N-C-C(CH ₃) ₃
30	1832	н₃со-{}-сн	2¯	1	2	0	R .	н	-CH ₂ -N-C-C(CH ₃) ₃
35	1833	H ₃ CQ - CH ₂ -	-	1	2	0	R	H	-CH ₂ -N-C
40	1834	HQ . H₃CO————————————————————————————————————	2-	1	2	0	R	н	-CH ₂ -N-C-(CH ₃) ₃
70	1835	но-{_}-сн₂	-	1	2	0	R	Н	-CH2-N-C-(CH3)3
45		CH ₂							-CH ₂ -N-C-C(CH ₃) ₃
50			•					н	-CH2-N-C-(CH3)3
									

Table 1.168

5	Compd. No.	R ¹ (CH ₂)	· -	k	m	n	chirality	R³	-(CH ₂) p R ⁴ R ⁵ (CH ₂) q G-R ⁶
10	1838	н₃сѕ-{_}-с	;H ₂ -	1	2	0	R	н	-CH2-N-C-(CH3)3
	1839	н₃ссн₂—С	CH₂−	1	2	0	R	н	-CH2-N-C-C(CH3)3
15	1840	о СН	s	1	2	0	R	H	-CH2-N-C-(CH3)3
20	1841	CH ₃	H2 -	1	2	0	R	н	-CH2-N-C-(CH3)3
25	1842	H₃C—(CH₃ H₃C	H ₂ -	1	2	0	R •	н	-CH2-N-C-(CH3)3
30	1843	(CH ₃) ₂ C H-√	CH _Z -	1	2	0	R	Н	-CH2-N-C-(CH3)3
35	1844	(CH ₃) ₃ C-	CH₂−	1	2.	0	Ŕ	н	-CH ₂ -N-C-(CH ₃) ₃
40	1845	H ₃ CCH ₂ —	CH₂ -	1	2	0	R	н	-cH2-NC
45	1846	H ₃ C · CH ₃	H ₂ –	1	2	0	R	н	-CH ₂ -N-C-SCF ₃
		(CH ₃) ₃ C						н	-CH ₂ -N-C-OCHF ₂
50	1848	H ₃ CQ HO	+ ₂ -	1	2	0	R	н	-сн- н с
55							· · · · · · · · · · · · · · · · · · ·		

Table 1.169

5	Compd. No.	R ¹ (CH ₂)	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1849	-CH ₂ -	1	2	0 -	R ·	н	-CH2-N-C-
15	1850	H₃CCH₂——————————————————————————————————	1	2	0	R	н	-сн₂-й с
	1851	CH ₃	1	2	0	R	н	- CH2-H C-
20	1852	CH₂-	1	2	0	R	н	-cH2-N.C-
25	1853	H ₃ CQ HO————————————————————————————————————	1	2	0	R .	н	-CH ₂ -N-C-
30	1854	CH₂-	1	2	O	R	н	-CH ₂ -N-C-
35	1855	 н₃ссн₂—Сн₂-	1	2	0	R	н	-CH ₂ -N-C-
40	1856	CH ₃				•	н	-CH ₂ -N-C
45	1857	CH₂-	1	2	0	R	н	-CH ₂ -N-C
50	1858	B(□) CH ₂	1	2	0	R	н	-CH ₂ -N-C-Br
	1859	H3CO-CH2-	1	2	0	R	н	-CH ₂ -N-C-Br
55					-		-	

Table 1.170

5	Compd.	R ¹ (CH ₂)-	k	m	n	chirality	R³ ·	$-(CH_2)_{p} + (CH_2)_{q} G - R^6$
10	1860	H ₃ CQ HO————————————————————————————————————	1	2	0	R	н	-CH ₂ -N-C-Br
	1861	HQ . H₃CO-CH₂-	1	2	0	R	н	-CH ₂ -N-C
	1862	HOCH ₂ -	1	2	0	R	Н	-CH ₂ -N-C
20	1863	CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
25	1864	H ₃ CS—CH ₂ —	1	2	0	R	Н •	-CH ₂ -N-C
30	1865	CH ₂ -	1	2	0	R 	н	-CH ₂ -N-C-Sr H ₂ N
35	1866	H_3C CH_3 CH_2 CH_2	1	2	0	R	Н	-CH ₂ -N-C-Br
40	1867	(CH ₃) ₂ C H- CH ₂ -	1	2	0	. R	Н	-CH ₂ -N-C
45	1868	(CH ₃) ₃ C————————————————————————————————————	1	2	0	R	н	-CH ₂ -N-C
50	1869	Br-CH ₂ -	1	2	0	R .	н	$-CH_2-NC$ H_2N
50	1870	H₃CO-{}-CH₂-	1	2	0	R	н	-CH ₂ -N-C
55		· · · · · · · · · · · · · · · · · · ·				-		

Table 1.171

5	Compd.	R ¹ (CH ₂) _j -	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q -G-R ⁶
10	1871	H ₃ CQ HO—CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
15	1872	HQ H ₃ CO- CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-
	1873	HO- (CH₂-	1	2	0	R	н	-CH ₂ -N-C-
20	1874	CH₂-	1	2	0	R	н	CH ₂ -N-C
25	1875	-CH ₂ -	1	2	. 0	R	н .	-CH ₂ -N-C
30	1876	H ₃ CS-CH ₂ -	1	2	0	R .	. H	-CH2-N-C-
35	1877	H ₃ CCH ₂ ————————————————————————————————————	1	2	0	R .	н	-CH ₂ -N-C
40	1878	CH₂-	1	2	0	R	H	-CH ₂ -N-C-
45	1879	H ₃ C ← CH ₂ − CH ₂ −	1	2	0	R	н	-CH ₂ -N-C-
50	1880	(CH ₃) ₂ CH-⟨)-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
	1881	(CH ₃) ₃ C-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
55								

Table 1.172

5	Compd. No.	R ¹ (CH ₂) _j	k	m	n	chirality	R ³	-(CH ₂) p G (CH ₂) q G-R 6
10	1882	B	1	2	0	R	н	-CH ₂ -N-C
15	1883	H₃CO	1	2	0	R	н	-CH ₂ -N-C-NO ₂
	1884	H ₃ CQ HO————————————————————————————————————	1	2	0	R	н.	-CH ₂ -N-C
20	1885	HQ H₃CO—CH₂-	1	2	0	R	н .	CH ₂ -N-C NO ₂
25	1886	HO- € -CH ₂	1	2	0	R	н	-CH ₂ -N-C NO ₂
30	1887	O-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
35	1888	CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
40	1889	H₃CS-CH₂-	1	2	0	R	н .	-CH ₂ -N-C-\ H ₂ N
45	1890	н₃ССН₂—(СН₂-	1	2	0	R	Н	H_2N O O O O O O O
50	1891	CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-NO ₂ H ₂ N NO ₂
	1892	CH ₃ H ₃ C-⟨	1	2	0,	R .	н	-CH ₂ -N-C
55								

Table 1.173

	Compd. No.	R ² (CH ₂)	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-P ⁶
	1893	CH ₃ -CH ₂ - H ₃ C	1	2 .	0	R	н	-CH2-N-C
	1894	(CH ₃) ₂ CH-€ CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
	1895	(CH ₃) ₃ C-{ CH ₂ -	1	2	0	R	H	-CH ₂ -N-C
	1896	HQ H₃CO—CH₂-		2	0	R	н	-CH ₂ -N-C
	1897	H₃CS-{\rightarrow}-CH2-	1	2	0	. R	н	-CH ₂ -N-C
	1898	H ₃ CCH ₂ —CH ₂ -	1	2	0	R	н	-CH ₂ -N-C- H ₂ N
	1899	(CH ₃) ₂ C H-CH ₂	1	2	0	R	н	-CH ₂ -N-C OCF ₃
·	1900	H ₃ CQ HO————————————————————————————————————	1	2	0	R	н	-CH ₂ -N-C
	1901	<u>ң</u> с(сң);—()-сң-	1	2	0	Ŗ	н	-CH ₂ -N-C
	1902	\sim	1	2	0	R	н	-CH ₂ -N-C-OCF ₃ H ₂ N
	1903	(CH ₃) ₂ CH-CH ₂ -	2	2	1	-	н	-CH ₂ -N-C

Table 1.174

5	Compd.	R ¹ (CH ₂)	k	m	n	chirality	R³	-(CH ₂) p G (CH ₂) q G-R ⁶
10	1904	H ₃ C(CH ₂) ₂	2	2	1	<u>-</u>	н	-CH ⁵ -N-C-\ OCE ³
15	1905	CI—CH ₂ —	1	2	0	R	н	-CH ₂ -N-C
	1906	CH ₂ -	1	2	0	. Я	н .	-CH ₂ -N-C
20	1907	но-(сн ₂ -	. 1	2	0	R	н	-CH ₂ -N-C-OCF ₃
25	1908	H ₃ CO-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
30	1909	H ₂ C=CH-CH ₂ -	1	2	0	. R	н	-CH ₂ -N-C
35	1910	Br—CH ₂ —	2	2	1	•	н	$-CH_2-N$ H_2N OCF_3
40	1911	CH2−	2	2	1	, •	н	-CH ₂ -N-C
45	1912	HO-CH ₂ -	2	2	1	-	н	$-CH_2-N$ C H_2N
50	1913	CH ₃ H ₃ C ← CH ₂ -	2	2	1	-	н	$-CH_{2}-N$ $-CH_$
	1914	H ₃ C-CH ₂ -	2	2	1	•	н	-CH ₂ -N-C
55							 	

Table 1.175

5	Compd.	R ¹ (CH ₂);-	k	m _.	ņ	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1915	H3CCH2Q H0-CH2-	1	2	0	R	н	-CH ₂ -N-C
15	1916	H ₃ C	1	2	0	R	н	-CH ₂ -N-C-OCF ₃
20	1917	HO-CH2-	2	2	1	-	н	-CH2-N-C
20	1918	H ₃ C HO—CH ₂ —	2	2	1		н	-CH ₂ -N-C
25	1919	CH-CH ₂ -	2 .	2	1	-	Н	-CH ₂ -N-C
30	1920	CH-CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
35	1921	CH_CH ₂ -		2	0	R	, н	-CH ₂ -N-C
40	1922	CH2-	2	2	1	-	H	-CH ₂ -N-C
45	1923	Br-CH ₂ -	2	2	1	-	н	-CH2-NC-SCF3
50	1924	H₃CO-(2	2	1	-	H	-CH ₂ -N-C-SCF ₃
55	1925	F-CH ₂ -	2	2 .	1	•	н	-CH ₂ -N-C-SCF ₃

Table 1.176

5	Compd.	R1 (CH ₂)-	k	m	n	chirality	Ŕ³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1926	F-CH ₂ -	2	2	1	-	н	-CH ₂ -N-C-SCF ₃
15	1927	но-{	2	2	1	-	н	-CH ₂ -N-C-SCF ₃
20	1928	CH₂-	2	2	1	-	н .	-CH2-N-C-SCF3
20	1929	CH₂-	2	2	1.	-	н	-CH ₂ -N-C-SCF ₃
25	1930	н₃СS-{¯}-СН ₂ -	2	2	. 1	- ···	H .	-CH ₂ -N-C-SCF ₃
30	1931	H ₃ CCH ₂ —CH ₂ -	2	2	1	•	Н	-CH ₂ -N-C-SCF ₃
35	1932 .	CH2-	2	2	1	-	н	-CH ₂ -N-C-SCF ₃
40		H ₃ C-CH ₂ -				-	H	-CH ₂ -N-C-SCF ₃
45	1934	CH ₃ H ₃ C — CH ₂ -	2.	2	1	-	н	-CH ₂ -N-C-SCF ₃ -CH ₂ -N-C-SCF ₃ -CH ₂ -N-C-SCF ₃ -CH ₂ -N-C-SCF ₃
50	1935	02 N-CH2-	2	2	1	-	н	-CH ₂ -N-C-SCF ₃
55	1936	H ₃ CCH ₂ -	2	2	1	-	н	-CH ₂ -N-C-SCF ₃
23								

Table 1.177

5	Compd. No.	R ¹ /(CH ₂) _j -	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1937	(CH ₃) ₂ C H ← CH ₂ -	2	2	1	- .	н .	- CH ₂ -N-C
15	1938	Br—€ CH ₂ -	2	2	1	•	H	-СH ₂ -N-С
	1939	H ₃ CO-CH ₂ -	2	2	1		н	сн ₂ -м-с
20	1940	F-CH ₂ -	2	2	1		н	-CH ₂ -N-C- H CH ₃
25	1941	F-CH2-	2	2	1		н	-СH ₂ -N-С
30	1942	HO-CH ₂ -	2	2	1	-	н	-сн ₂ -N-с
35	1943	CH ₂ -	2	2	1	-	н.	- CH ₂ -N-C
40	1944	-CH ₂ -	2	2	1	-	н	-CH2-N-C
45	1945	H3CS-(2	2	1	-	н	-CH2-N-C-CH3
50	.1946	H ₃ CCH ₂ —CH ₂ -	2	2	1	-	H	-CH ₂ -N-C-\CH ₃
50								-CH2-N-CShr CH3-CH3
55								

Table 1.178

5	Compd.	R ¹ (CH ₂) _j -	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
	No.	R"						R ³
10		CH ₃ CH ₂ −					н	-CH ₂ -N-C
15	1949	CH ₃ -CH ₂ -	2	2	1	-	н	-CH2-N-C- Br CH3
	1950	0 ₂ N-CH ₂ -	2	2	1	-	н	-CH2-N-C-Br
20	1951	H₃C-{	. 2	2	1	-	н	-CH ₂ -N-C
25	1952	Вг—СН ₂ -	2	2	1	-	н	-CH ₂ -N-C
30	1953	H3CO-CH2-	2	2	1	-	H	-CH ₂ -N-C
35	1954	F-CH2-	2	2	1	-	н	-CH ₂ -N-CF
40	1.955	F-CH ₂ -	2	2	1	<u>-</u> ·	н	-CH ₂ -N-C
45	1956	HO-CH2-	2	2	1	-	Н	-CH ₂ -N-C
50	1957	CH₂-	2	2	1	•	н	-CH2-N-C
55	1958	CH₂-	2	2	1	-	н	-CH ₂ -N-C-C-F
<i>55</i>								

Table 1.179

5	Compd.	R ¹ (CH ₂) _j -	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1959	H ₃ CS-()-CH ₂ -	2	2	1	•	н	-CH ₂ -N-C
15	1960	H ₃ CCH ₂ ————————————————————————————————————	2	2	. 1	-	Ĥ,	-CH ₂ -N-C
,,	1961	CH₂-	2	2	1	-	н	-CH ₂ -N-C-Sr
20	1962	H ₃ C-⟨CH ₃ -CH ₂ -	2	2	1	-	н	-CH₂-N-CSPr
25	1963	H ₃ C — CH ₂ — CH ₂ — CH ₂ —	2	2	1	-	н	-CH ₂ -N-C
30	1964	O ₂ N-CH ₂ -	2	2	1		н	-CH ₂ -N-C
35	1965	H ₃ C-CH ₂ -	2	2	1	-	н	-CH₂-N-C-SF
40	1966	(CH ₃) ₂ CH————————————————————————————————————	2	2	1	-	н	-CH ₂ -N-C
45	1967	Br—CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
22	1968	H₃CO-{}-CH₂-	2	2	1	-	н	-CH ₂ -N-C
50	1969	HO-CH2-	2	2	1	-	н	-CH ₂ -N-C
55			-			·		

Table 1.180

5	Compd.	R ¹ (CH ₂)j-	k	m	n	chirality	H3	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1970	CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
	1971	CH₂-	2	2	1	-	н	-CH ₂ -N-C
15	1972	H₃CS-CH₂-	2	2	1	-	н	-CH ₂ -N-C
20	1973	H ₃ CCH ₂	2	2	1	-	н	-CH ₂ -N-C
25	1974 ·	CH ₃	2	2	1		. H	-CH ₂ -N-C
30	1975	O ₂ N-CH ₂ -	2	2	1		н	-CH ₂ -N-C
35	1976	H₃C-(CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
40	1977	NC-CH2-	2	2	1		н	-CH ₂ -N-C
45	1978	(снэ)2с н-С	2	2	1	-	н	-CH ₂ -N-C
-								
50	1980	-CH ₂ -	2	2	1	-	н	$-CH_{2}-N-C$ $-CH_{2}-N-C$ $+CH_{2}-N-C$
55								

Table 1.181

5	Compd. No.	R^{1} $(CH_{2})_{j}$	k	m	n	chirality	Ŕ³	$-(CH_2)_{p} + (CH_2)_{q} - G-R^6$
10	1981	0 ₂ N-CH ₂ -	2	2	1	•	н	-CH ₂ -N-C
	1982	NC-CH2-	2	2	1	-	н	-CH ₂ -N-C
15	1983	(CH3)2CH-CH2-	2	2	1	-	н	CH ₂ -N-C
20	1984	Br—CH₂−	2	2	1	-	н	-CH ₂ -N-C-
25	1985	H ₃ CO-CH ₂ -	2	2	1	•	. н	-CH ₂ -N-C-
30	1986	HO-CH ₂ -	2	2	1	-	H	-CH ₂ -N-C
35	1987	СН₂-	2	2	1		н	-CH ₂ -N-C
40	1988	CH2-	2	2	1	•	н	-CH ₂ -N-C
45	1989	H ₃ CS-CH ₂ -	2	2	1	٠	н	-CH ₂ -N-C-
•	1990	H ₃ CCH ₂ —CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
50	1991 [.]	CH ₂ -	2	2	1	-	н	-CH2-N-C-
55								

Table 1.182

5	Compd.	R ¹ (CH ₂	.) _i	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	1992	H ₃ C-CH	3 CH ₂ -	2	2	1	-	н	-CH ₂ -N-C-
	1993	02 N	CH₂–	2	2	1	-	. H	-CH ₂ -N-C
15	1994	H ₃ C-\	CH2−	2	2	1	-	н	-CH ₂ -N-C
20	1995	NC-()	CH2-	2	2	1	-	н	-CH ₂ -N-C-
25	1996	(CH ₃) ₂ CH-	-СН2-	2	2	1	-	H .	-CH ₂ -N-C
30	1997	H ₃ C	3 CH ₂ –	2	2	1	-	н	-CH ₂ -N-C
35	1998	8	H ₂ -	2	2	1	-	н	-CH2-N-C-
40	1999	н₃со-{}-	CH₂-	2	2	1	-	н	-CH ₂ -N-C-C
	2000	F—C	H ₂ -	2	2	1	•	н .	-CH ₂ -N-C-
45	2001	но-{-}-с	;H ₂ −	2	2 .	1	-	н	-CH2-N-C-C
50									-CH2-N-C-

Table 1.183

5	Compd.	R ¹ (CH ₂) _j -	k	m	n	chirality	. R ³	$-(CH_2)_{p} + (CH_2)_{q} - G - R^6$
10	2003	CH ₂ -	2	2	1	_	Н	-CH2-N-C-€
15	2004	H ₃ CS−CH ₂ −	2	2	1		н	-CH ₂ -N-C-
,3	2005	н₃ссн₂—Сту-сн₂-	2	2	1	-	н	-CH2-N-C-
20	2006	CH ₃	2	2	1	-	н	-CH2-N-C-
25	2007	0 ₂ N-CH ₂ -	2	2	1	-	н .	-CH2-N-C-
30	2008	H ₃ C-(CH ₂ -	2	2	1	-	н	-CH2-N-C-
35	2009	NC-{\rightarrow}-CH2-	2	2	1	-	н	-CH ₂ -N-C-CI
40	2010	(CH ₃) ₂ C H-√CH ₂ -	2 .	2	1	· -	н	-CH ₂ -N-C-
45	2011	H ₃ C — CH ₂ — CH ₂ —	2	2	1	-	н	-CH,-NC
45	2012	Br-CH ₂ -	2	2	• 1	-	н	-CH ₂ -N-C
50	2013	H3CO-(2	2	1	•	н	-CH2-N-C
								

Table 1.184

5	Compd. No.	R ¹ (CH ₂),-	k	m	n	chirality	R ³	—(CH ₂) _p + (CH ₂) _q G-R ⁶
10	2014	HO-{CH ₂ -	2	2	1	:	н	-CH₂-N-CS-CI
	2015	CH ₂ -	2	2	1	- ,	H	-CH2-N-C-Br
15	2016	-CH ₂ -	2	2	1.	-	H	-CH ₂ -N-C
20	2017	H₃CS-CH₂-	2	2	1	-	н	-CH2-N-C-Sa
25	2018 ,·	H ₃ CCH ₂ —CH ₂ -	2	2	1	-	н.	-CH ₂ -N-C
30	2019	-CH _Z	2	2	1	-	H	-CH ₂ -N-C
35	2020	. СН ₃	2	2	1	-	н	-CH ₂ -N-C- HC-CH Br CI
40	2021	0 ₂ N-CH ₂ -	2	2	1	-	н	-CH ₂ -N-C-SBr
45	2022	H₃C-CH₂-	2	2	1	-	н	-CH ₂ -N-C-Sar
	2023	NC—CH₂-	2	2	1	-	H .	-CH ₂ -N-C-Shr H C-Sh-Cl
50	2024	(CH ₃) ₂ CH−СH ₂ −	2	2	1		н	-CH₂-N-C-S-CI
								

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Table 1.185

5	Compd. No.	R ¹ (CH ₂)- "	k	m	n	chirality	R³	-(CH ₂) - + (CH ₂) - G-R ⁶
10	2025	H ₃ C CH ₂ - H ₃ C	2	2	1	-	Н	-CH ₂ -N-C
	2026	F-CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
15	2027	ВСН₂-	2	2	1	-	н	-CH ₂ -N-C-Br
20	2028	H₃CO-{CH ₂ -	2	,2	1	-	н	-CH ₂ -N-C
25	2029	но-{_}-сн₂-	2	2	1	-	н	-CH ₂ -N-C-Br
30	2030	CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
35	2031	CH ₂ -	2	2	1	-	н	-CH ₂ -N-C-Br
	2032	CH _Z	2	2	1	٠	н	-CH ₂ -N-C-Br
40	2033	сн ₃ -сн ₂ -	2	2	1	-	H	-CH ₂ -N-C
45	2034	02 N-{-}-CH2-	2	2	1	-	н	-CH ₂ -N-C-Br
50	2035	H ₃ C-{	2	2	1	-	н	-CH ₂ -N-C
								_

Table 1.186

5	Compd.	R ¹ (CH ₂)j-	k	m	n	chirality	R³	$-(CH_2)_{\overline{p}} + (CH_2)_{\overline{q}} - G - R^6$
٠.	2036	NC-CH ₂ -	2	2	1	•	н	-CH ₂ -N-C
10	2037	CH ₃ H ₃ C ← CH ₂ -	2	2	1	-	н	-CH ₂ -N-C-Br
15	2038	F—CH2-				-	ıн	-CH ₂ -N-C
20	2039	H3C-CH2-	2	2.	1	-	 Н	-CH ₂ -N-C- H CN
25	2040	H ₃ C-←CH ₂ -	1	2	0	R	н .	-cH2-N-C-CH-
30	2041	H₃C-(-)-CH ₂ -	1	2	0	R	. H	Q QCH ₃ −CH ₂ −N-C-CH
35	2042	H ₃ C-CH ₂ -	1	2	0	R	н	-CH2-N-C
33	2043			2	0		н	-CH ² -M-C-CH ² CH ³
40	2044	CH ₃	1	2	0	R	. Н	-CH2-N-C-()-O-()
45	2045	CH ₃ N CH ₂ - CH ₃	1	2	0	R	н	-cH2-H-C-M-CI
50	2046	CH ₃ CH ₂ - CH ₃	1	2	0	R	н	-CH ₂ -N-C-D-O-O-O-O-O-O-O-O-O-O-O-O-O-O-O-O-O-O
								· · · · · · · · · · · · · · · · · · ·

Table 1.187

5	Compd.	R (CH ₂) _j -	k	m	n	chirality	R ³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	2047	CH ₃ CH ₂ CH ₃	1	2	0	R	н	-си- н с
	2048	CH ₃ N CH₂- CH₃	1	2	0	R	н	-cH ₂ -N-c
15	2049	CH ₃ CH ₂ - CH ₃	1	2	0	R	н .	-CH-NC-CHs
20	2050	H ₃ C S CH ₂ -	1	2	0	R	H	-сн ₂ -м-с-
25	2051	H ₃ C CH ₂ -	1	2	0	R	н	· -сн ₂ -N-с
30	2052	Bt CH₂− OCH₂CH₃	2	2	1	-	н	-CH ₂ -N-C
35	2053	н ₃ со Сн ₂ о — Сн ₂ -	2	2	1	-	н	-CH2-N-C-F H
	2054	H ₃ CO-CH ₂ -					Н	-CH2-N-C-F
40	2055	H₃CQ CH₂- OH	2	2	1	<u>:</u>	. Н	-CH ₂ -N-C
45	2056	Bs CH ₂ -	2	2	1	-	н	-CH ₂ -N-C-F H ₂ N
50		H ₃ CO-CH ₂ -						-CH ₂ -N-C-F
								

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Table: 1.188

5	Compd.	R ¹ (CH ₂)j-	k	m	n	chirality	R³	−(CH ₂) p (CH ₂) q G−R ⁶ . R ⁵
10	2058	H ₃ CO OCH ₃	2	2	1	•	н	-CH ₂ -N-C
	2059		2	2	1	-	Н	-CH ₂ -N-C
15	2060	H ₃ CO CH ₂ - OCH ₃	2	2	1		H ,	-CH ₂ -N-C-F H ₂ N
20	2061	F CH ₃ CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
25	2062	H3CO- CH2-	2	2	1	-	н	-CH ₂ -N-C-F H ₂ N
30 _.	2063	H₃CQ H₃C————————————————————————————————————	2	2	1	· -	н	- CH ₂ -N-C
35	2064	BI CH2	2	2	1	-	н	-CH ₂ -N-C
	2065	H3CCH2O-CH2-	2	2	1	-	н	-CH ₂ -N-C
· 40	2066	OCH ₂ -CH ₂ -	2	2	1	-	н	-CH ₂ -N-C-F
45	2067	(HC)3CHCH	2	2	1	•	, н	-CH ₂ -N-C
50								-CH ₂ -N-C-F H ₂ N

Table 1.189

Compd.	R ¹ (CH ₂) _j	k	m	'n	chirality	R ³	-(CH ₂) p C CH ₂)q G-R ⁶
2069	H ₃ CO	2	2	1	•	н	-CH ₂ -N-C
2070	Br CH2- OCH3	2	2	1	-	н .	-CH ₂ -N-C
2071	H₃CO-{CH₂- OCH₃	2	2	1	-	н	-CH ₂ -N-C
. 2072	(H ₃ C) ₂ CHO-{	2	2	1	-	н	-CH ₂ -N-C
2073	CH ₂ Q CH ₂ -CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
	н,со-О-О-Сну-				4 *	. Н	-CH ₂ -N-C
2075	H ₃ CQ CH ₂ -	2	2	1	-	Н	-CH ₂ -N-C
2076	F-CH ₂ -	2	2	1	-	н	-CH2-N-C-F
	CI CH₂- OH						-CH ₂ -N-CF H ₂ N
2078	H ₃ CCH ₂ Q OH CH ₂ -	2	2	1	<u>-</u>		-CH ₂ -N-C
2079	СН ₂ О H ₃ CO-СН ₂ -	2	2	1	-	, н	-CH ₂ -N-C

Table 1.190

Compd.	R ² (CH ₂) _j	k	m	n ct	nirality	R³	$-(CH_2)^{-\frac{R^4}{p}+}_{p}(CH_2)^{-\frac{1}{q}}G^-R^6$
2080	СH2Q H3CO—СH2-	2	2	1.	•	н	-CH ₂ -N-C
2081	CL HO—CH ₂ -	2	2	1 ·	-	н	-CH ₂ -N-C
2082	OH H₃CO-⟨CH₂-	2	2	1	- .	н	-CH ₂ -N-C
2083	H ₃ CQ HO———CH ₂ —	1	2	0	R	н	-CH _{2-N-} C
2084	H ₃ CO CH ₂ -	1	2	0	R	н	-CH _{2-N} -CF ₃
2085	OH -CH2-	1	2	0	R	• H	-CH ₂ -N-C
2086	CI HO—CH ₂ —	1	2	0	R	н	-CH ₂ -N-C-S
2087	(H ₃ C) ₂ N-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃
2088	(H3CCH2)2N-CH2-	1	2	0	R	н	H ₂ N CF ₃ -CH ₂ -N-C- H ₂ N
2089	F-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-
2090	CH₂	1	2	0	R	н	-CH ₂ -N-C-CF ₃

Table 1.191

5	Compd. No.	R ¹ (CH ₂)	·k	m	n	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} - G-R^6$
10	2091	с⊢-{}-сн₂-	2	2	1	-	н	-CH-N-C
15	2092	CH_CH2-	2	2	1	- .	н	OH NO CHOCHS
13	2093	СI—СН ₂ -	2	2	1	-	н	(F) 0 OCH₂CH₃ -CH-N-C- H CH₂CH₂SCH₃
20	2094	CH2-CH2-	2	2	1	-	н	CH2 3
25	2095	CI—CH ₂ -	2	2	1	-	, н	(R) OCH₂CH₃ -CHN-C- H C(CH₃)₃
30	2096	С⊢-{}-СН₂-	· 2	2	. 1 .		· H ·	(R O OCH ₂ CH ₃ -CH N C
35	2097	С⊢—СН₂-	2	2	1	-	н	(A) OCH ₂ CH ₃ OC
40	2098	с⊢—СН₂-	2	2	1	-	H	CH-N-C-CI
40	2099	. СНСН₂-	2	2	1	-	н	-CHH C
45	2100	СН-СН2-	2	2	1	-	н	CH-N-C-OCH ₃
50	2101	сн-Сн2-	2	2	1	•	н	', O DCH₂CH₃
								<u> </u>

Table 1.192

5	Compd.	R1 (CH2)-	k	m	'n	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} - G-R^6$
10	2102	CH-CH2-	2	2	1	-	Н	-CH-N-C-C-OCH2-CH3 -CH2CH2-C-OCH2-CH3
	2103	CH2-	2	2	1	-	н	() OCH2CH3 -CHN-C-
15 ,	2104	CI—CH2-	2	2	1	-	н	CH2CH2COCH3
20	2105	H ₃ CO OH	2	2	1	-	н	-CH ₂ -N-C
25	2106	H ₃ C OH CH ₂ -	. 2	2	1	-	н	-CH ₂ -N-C
30	2107 [.]	Br CHz-	2	2	1	-	· н	-CH ₂ -N-C
<i>35</i>	2108	CH ₃ CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
	2109	Br CH2	2	2	1	-	н	-CH ₂ -N-C
40	2110	H3CCH2 CH2-	2	2	1	-	н	-CH ₂ -N-C
45	2111	CH2-	2	2	1	-	н	-CH ₂ -N-C
50							н	-CH ₂ -N-C

Table 1.193

	Compd. No.	R^1 $(CH_2)_j$	k	m	n	chirality	R³	$-(CH_2)_{p}$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
	2113	H ₂ N H ₃ CO-CH ₂	2	2	1	-	Н	-CH ₂ -N-C
ı	2114	H ₂ N H ₃ C—CH ₂ -	2	2	1	-	н	-CH ₂ -N-C-F H ₂ N
	2115	CH-{	2	2	1	-	H	(F) OCH ₂ CH ₃ -CH-N-C
1	2116	C├ - ()-CH ₂ -	2	2	. 1	-	н	(<i>F</i>) OCH ₂ CH ₃ -CH-N-C
;	2117	с⊢СН₂-	2	2	1	• -	H	CH2-NH
,	2118	HO—CH ₂ —	1	. 2	0	В	-Н	-CH ₂ -N-C-(-) H ₂ N
i	2119	· OH	1	2	0	R	н	-CH ₂ -N-C
ı	2120	Br	1	2	0	R	Н	-CH ₂ -N-C
·	2121	OCH ₃	1	2	0	R	н	H_2N CF_3 $-CH_2-N-C$ H_2N CF_3
		CH2−					н	-CH ₂ -N-C
1	. 2123	O CH₂- NO₂	1	2	0	R	н	H_2N $-CH_2-N-C$ H_2N $-CH_2-N-C$ H_2N $-CH_2-N-C$ H_2N
;								

Table 1.194

Compd.	R ¹ (CH ₂) _j -	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
2124	O ₂ N Cl—CH ₂ -	1	2	0	R	Н	-CH ₂ -N-C
2125	O ₂ N CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
2126	O ₂ N H ₃ C————————————————————————————————————	1	2	0	R	н	-CH ₂ -N-C
2127	CH ₂ -	1	2	0	Я	н	-CH ₂ -N-C
2128	H ₂ N H ₃ CO CH ₂	1.	2	0	R	H,	-CH ₂ -N-C
2129	H ₂ N H ₃ C-CH ₂ -	. 1	2	0	R	н	-CH ₂ -N-C
2130	0- N CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
2131	CH ₃ CH ₃	2	2	1		Н	-CH2-N-C
2132	H ₂ N CH ₂ —CH ₂ —	1	2	0	R	н	-CH ₂ -N-C
2133	(H ₃ C) ₂ N CH ₂ —CH ₂ —					н	-CH ₂ -N-C- H ₂ N CF ₃ -CH ₂ -N-C- H ₂ N
2134	O CH ₂ - N(CH ₃) ₂	1	2	0	R	н	-CH ₂ -N-C

Table 1.195

Compd.	R ¹ (CH ₂)	k	m	n	chirality	R³	$-(CH_2)_{\overline{p}} + (CH_2)_{\overline{q}} - G - R^6$
2135	(H ₃ C) ₂ N H ₃ CO————————————————————————————————————	.1	2	0	R	Н	-CH ₂ -N-C
2136	(H ₃ C) ₂ N H ₃ C — CH ₂ -	1	2	0	R	н	- CH ₂ -N-C
2137	CH ₃	1	2	0	R	н ,	CH ₂ -N-C
2138	CH3 CH3	1	[.] 2	0	R	н	-CH ₂ -N-C
2139	H ₃ C. CI CH ₂ -CH ₂ -	. 1	2.	0	R	H	-CH ₂ -N-C
2140	CH ₂ -	. 2	2	- 1.	.	⊹. Н	CH ₂ N-C-F H ₂ N
2141	HO—CH ₂ -	2	2	1	-	H	-CH ₂ -N-C
2142	H ₂ N CH ₂ -CH ₂ -	2	2	1	-	н	-CHN-C
2143	HNG-CH3	2	2	1	-	н	-CH ₂ -N-C
2144	H ₂ N H ₃ CO-CH ₂ -	.2	2	1	-	н	-CH ₂ -N-C
2145	H ₂ N HO—CH ₂ -	2	2	1		н	-CH ₂ -N-C

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5	Compd. No.	R ¹ (CH ₂),-	k	m	n	chirality	R³	-(CH ₂) p (CH ₂) q -G-R ⁶
10	2146	CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
15	2147	H ₃ C-C-NH H ₃ CO-CH ₂ -	2	2	1	•	н	-CH ₂ -N-C
	2148	H ₃ C-C-NH HO-CH ₂ -	2	2	1		н	-CH ₂ -N-C
20	2149	HO-CH ² -	1	2	0	R	.	-CH ₂ -N-C
25	2150	H ₃ C-C-NH CI	1	2	0	R	н	-CH ₂ -N-C
30	2151	HMC-CH ³	1	2	0	· · · R···	… н	-CH ₂ -N-C
35	2152	H ₃ C-C-NH H ₃ CO-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
40	2153	H ₃ C-C-NH H ₃ C-C-CH ₂ -	. 1	2	0	R	н	-CH ₂ -N-C
45	2154	H ₃ C-C-NH H ₃ CO-CH ₂ -	2	. 2	1		н .	-CH ₂ -N-C
	2155	H3 C-C-NH H0-CH2-					н	-CH ₂ -N-C-CF ₃
50	2156	HMC-CH2	2	2	1	· .	н	-CH2-N-C-CF3
55								

T	a	h	le	1	1	9	7

								A
5	Compd. No.	R ² (CH ₂) _j -	k	m [°]	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	. 2157	HO-{CH ₃	1	2	0	R .	н	-CH ₂ -N-C
15	2158	H ₃ C-NH HO———————————————————————————————————	1	2	0	R	н	-CH ₂ -N-C
,,	2159	H ₃ C-NH H ₃ CO-CH ₂ -	2	2	· 1	-	н .	-CH ₂ -N-C
20	2160	H ³ C-NH	2	2	1	-	н	-CH ₂ -N-C
25	2161	H³C-NH CH²-	2	2	1	• <u>•</u>	н	-CH ₂ -N-C-F H
30	2162	H ₃ C-NH H ₃ CO CH ₂ -	2	. 2	1.		· н	-CH ₂ -N-C
35	2163	H ₃ C-NH HO-CH ₂ -	2	2	1	-	н	H ₂ N -CH ₂ -N-C
40	2164	CH3 CH3	1	2		R	• н	-CH ₂ -N-C-S H ₂ N
	2165	H N CH₂-	1	2	0	R	н .	-CH ₂ -N-C
45	2166	CS CH2-	1	2	0	R	н	-CH ₂ -N-C- H ₂ N -CH ₂ -N-C- H ₂ N -CH ₃ -N-C- H ₂ N
50	· 2167	H CH2	1	2	0	R	. Н	-CH ₂ -N-C-CF ₃

Table 1.198

5	Compd. No.	R ¹ (CH ₂),-	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	2168	H ₃ C CH ₃	1	2	0	R	н	-CH ₂ -N-C
15	2169	н ₃ с-{ СН ₃ СН ₃ СН ₃	1	2	0	R	н	-CH ₂ -N-C
	2170	C) CH,-	1	2	0	R	н	-CH ₂ -N-C
20	2171	H ₃ C CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
25	2172	F ₃ CH ₂ CH ₂ CH ₃	1	2	0	R	н	-CH ₂ -N-C
30 .	2173	S CH ₂ - CH ₃	1.	2	0	R	н	-CH ₂ -N-C-CF ₃
35	2174	H ₃ C CH ₃	1	2	0	R	н	-CH ₂ -N-C-CF ₃
40	2175	OCH ₃					н	-CH ₂ -N-C-√S
	2176	H ₃ C'N - CH ₂ -	1	2	0	R	Н	-CH ₂ -N-C-CF ₃ H ₂ N
45	2177	H ₃ COH CH ₂ CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-CF ₃ .
50	2178	H ₂ CO-C	1	2	0	R	н	-CH ₂ -N-C
				·				

Table 1.199

5	Compd. · No.	R ¹ (CH ₂),	k	m	n	chirality	R³	$-(CH_2)_p + (CH_2)_q G - R^6$
10	2179	н3с-6-и -сн3-	1	2	0	R	н	-CH ₂ -N-C
15	2180	C-(CH ₂) ₂ -	1	2	0	R	н	-CH ₂ -N-C
	2181	H ₃ CO N CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
20	2182	H ₃ C N CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
25	2183	5-N_CH2-	1	2	0	R	• н	-CH ₂ -N-C
30	2184	S-N N-CH ₂ -	2	2	1.	-	н	-CH ₂ -N-CF H ₂ N
35	2185	5-N CH ₂ -	2	. 2	1	-	н	-CH ₂ -N-C
40	2186	H N N CH₂-	2	2	. 1	· •	н .	-CH ₂ -N-C- H ₂ N
	2187	H ₂ N HO————————————————————————————————————	1	. 2	0	R	н	-CH ₂ -N-C
45	2188	CH ₂	2	2	1	-	Н	-CH ₂ -N-C-CF ₃
50	2189	CH2-CH2	1	2	0	R	н	-CH ₂ -N-C- H ₂ N CF ₃ -CH ₂ -N-C- H ₂ N CF ₃ -CH ₂ -N-C- H ₂ N CF ₃
								·

Table 1.200

5	Compd. No.	R ¹ (CH ₂) _j	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	2190	CH₂-	2	2	1	-	н	-CH ₂ -N-C
15	2191	CH2-	2	2	1	•	н	-CH ₂ -N-C
	2192	S H CH2-	2	2	1	•	н	-CH ₂ -N-C
20	2193	CH²-	2	2	1	-	н	-CH ₂ -N-C
25	2194 ·	H ₂ N H ₃ C-CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
30	-2195	H ₂ N CI—CH ₂ -	2	2 ·	1.	. ₽ 	· . н	-CH ₂ -N-C
35	2196	H ₃ C-NH H ₃ C-CH ₂ -	1	2	0	R	н	-CH2-H C
40	2197	H ₃ CO-NH H ₃ CO-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
45	2198	H ₃ C-NH CH2-CH ₂ -	1	2	0	Я	н	-CH ₂ -N-C
	2199	H ₃ C-NH H ₃ C-CH ₂ -	2	2	· 1	-	н	-CH ₂ -N-CCF ₃
<i>50</i>	2200	H ₃ C-NH CH ₂ -CH ₂ -	2	2 .	1	-	H	-CH ₂ -N-C-CF ₃
55								

Table 1.201

5	Compd.	R ¹ (CH ₂) _j -	k	m	n	chirality	R³	$-(CH_2)_{p} + (CH_2)_{q} - G-R^6$
10	2201	H ₃ C-NH H ₃ C-CH ₂ -	2	2	1	-	Н	-CH ₂ -N-C
15	2202	S H CH ₂	1	2	0	R	н	-CH ₂ -N-C
	2203	CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
20	2204	CH ₃	2	2	1	-	н	-CH ₂ -N-C
25	2205	CH ₃	2	2	1	-	н	-CH ₂ -N-C
30	2206	CH ₃	. 2	2	1	- 	H	-CH ₂ -N-C
35	2207	СН ₃	2	2	1	-	н	-CH ₂ -N-C-F H ₂ N
40		HN-CH3				-	н	-CH ₂ -N-C
45	2209	HN-CH ₃	2	2	1	-	н	-CH2-N-C
	2210	LH-CH ² -	1	2	0	R	н	-CH ₂ -N-CF ₃
50	2211.	CH ₂ -	2	2	1	· <u>-</u>	н	-CH ₂ -N-C-F ₃

Table 1.202

5	Compd. No.	R ¹ (CH ₂),—	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q -G-R ⁶
10	2212	CH2-	2	2	1	-	н	-CH ₂ -N-C
15	2213	H ₂ N CH ₂ -CH ₂ -	2	2	1	. •	н	-CH ₂ -N-C
20	2214	H ₂ N H ₃ C-CH ₂ -	2	2	1		н	-CH ₂ -N-C
20	2215	H ₃ C-HN C⊢CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
<i>25</i>	2216	H ₃ CCH ₂ CH ₂ -	1	2	0	R	н	-CH ₂ -N-O-CF ₃
30	2217	H ₃ CO-Ç CH ₂ -	1	2	0	R	H	-CH ₂ -N-C
35	2218	CHCH	1	2	0	R	н	H ₂ N -CH-H-CF3
40	2219	CH ₂ -	1	2	0	R	H	- ON THE CF3
45	2220	CH_CH2-	1	2	0	R	н	-CH2-NC-NCH3/2
	2221	CH_CH2-	. 1	2	0	R	н	-ch-ho-ch-
50	2222	H ₃ C CO ₂ CH ₃ CH ₂ - CH ₃ C CH ₃	1	2	0	R	н	-CH2-N-CF3
55								

Table 1.203

5	Compd. No.	R ¹ (CH ₂)j-	 k	m	n	chirality	R³	-(CH ₂) _p G-R ⁶
10	2223	C1—(CH ₂ -	1	2	0	R	н	-CH2-NC-NN CF3
15	2224	C⊢—CH₂-	1	2	0	R	н	-CH-N-CF3
13	2225	о—{	1	2	.0	R	н	-CH = H C N N CF3
20	2226	H ₃ C, CH ₂ - CH ₃ -	1	2	0	R	н	-CH ₂ -N-O
25	2227	CH2−CH2−	1	2	0	R	н	-сн- и с С Рэ ни 6 С Н — М(сны)2
30	2228	CH2−	1	2	0	R	H	-CH2-HO CF3
35	2229	CH ₃	1	2	0	, R -	н	-CH ₂ -N-C
40		H ₃ CCH ₂ CH ₃					н	-CH ₂ -N-CCF ₃
45	2231	H ₃ CO-CH ₂ -	1	2	0	R	н	-CH ₂ -N-CCF ₃
	2232	H ₃ CO—CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
50	2233	CH2 CH2	1	. 2	0	R	н	-CH ₂ -N-C- H ₂ N OCF ₃ OCF ₃ -CH ₂ -N-C- H ₂ N CF ₃ -CH ₂ -N-C- H ₂ N
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Table 1.204

5	Compd.	R ¹ (CH ₂)j-	k	m	n	chirality	R³	$-(CH_2)_{p} + \frac{R^4}{R^5} (CH_2)_{q} - G - R^6$
10	2234	CH ₂ - CH ₃ H	1	2	0	R	н	-CH _z -N-C
15	2235	CH Z	1	2	0	R	н	-CH ₂ -N-C
	2236	F CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-SOCF ₃
20	2237	CH2-	1	2	0	R	н	-CH ₂ -N-C-SOCF ₃
25	2238	H ₃ CQ CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
30	2239	CH3 CH2	1	2	0	R	н	-CH ₂ -N-C-S
35	2240	CH ₂ - CH ₃	1	2	0	R	н	-CH ₂ -N-C
40	2241	H ₃ C N H	1	2	0	R	н	-CH ₂ -N-C-SOCF ₃
45	2242	CH ₂ -	1	2	0	R ·	н	-CH ₂ -N-C
	2243	(H ₃ C) ₂ N-CH ₂ -	1	2	0	R	н	-CH ₂ -N-C
50	2244	F CHT	1	2	0	. R	н .	-CH ₂ -N-C
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Table 1.205

5	Compd.	R ¹ (CH ₂) _j -	k	m	n	chirality	R³	-(CH ₂) _p + (CH ₂) _q G-R ⁶
10	2245	H ₃ C N CH ₂	1	2	0	R	н	-CH ₂ -N-C
15	2246	Haccha Haccha	1	2	0	R	н	-CH ₂ -N-C
	2247	(HC)2CH N CH-	1	2	0	R	н	-CH ₂ -N-C-CF ₃
20	2248	H ₂ N CH ₂ -	1	2	0	R	н	-CH ₂ -N-C-S-H ₂ N
25	2249	H ₂ N H ₃ CO-CH ₂ -	1	2	0	R	н	-CH2-N-C-OCF3
30	2250	H ₂ N HO-CH ₂ -	. 1	2	0 ·	R .	H	-CH ₂ -N-C
35	2251	H ₂ N H ₃ C-CH ₂ -					н	-CH ₂ -N-C
40	2252	CH ₂ -	2	2	1	-	н	-CH ₂ -N-C-CF ₃
45	2253	F CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
	2254	H₃CO CH₂-	·2	2	1	-	н	-CH ₂ -N-C
50	2255	H ₃ C CH ₂ -	2	2	1	-	н	-CH ₂ -N-C
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Table 1.206

Compd. No.	R^1 $(CH_2)_j$	 k	m	n	chirality	R³	$-(CH_2)_{p}$ $+\frac{R^4}{R^5}(CH_2)_{q}$ $-G^-R^6$
2256	CH ₂ -	2	2	1	•	н	CH ₂ -N-C
2257	H ₃ CQ CH ₂ -	2	2	1	-	н	-CH ₂ -N-C-S

the acid include a mineral acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid or carbonic acid and an organic acid such as maleic acid, citric acid, malic acid, tartaric acid, fumaric acid, methanesulfonic acid, trifluoroacetic acid or formic acid.

[0096] Furthermore, C₁-C₆ alkyl addition salts of the cyclic amine compounds, for example, 1-(4-chlorobenzyl)-1-methyl4-[{N-(3-trifluoromethylbenzoyl)glycyl}aminomethyl]piperidinium iodide are also used in the present invention. The alkyl group preferably includes methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, neopentyl, tert-pentyl, 2-methylpentyl and 1-ethylbutyl herein; however, methyl group, ethyl group or the like is especially preferable. A halide anion such as fluoride, chloride, bromide or iodide is preferable for a counter anion of an ammonium cation.

[0097] In the present invention, a racemate and all the possible optically active forms of the compounds represented by the above formula (I) can also be used.

[0098] The compounds represented by the above formula (I) can be synthesized by using any of the following general preparation processes described in WO9925686:

(Preparation process 1)

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[0099] A preparation process comprises reacting one equivalent of a compound represented by the following formula (II):

wherein R^1 , R^2 , R^3 , j, k, m and n are each the same as defined in the above formula (I), with 0.1 to 10 equivalents of a carboxylic acid represented by the following formula (III):

$$\begin{array}{c} O \\ HO - C - (CH_2)_p - \frac{R^4}{R^5} (CH_2)_q - G - R^6 \end{array}$$
 (III)

wherein R⁴, R⁵, R⁶, G, p and q are each the same as defined in the above formula (I), or a reactive derivative thereof in the absence or presence of a solvent.

[0100] The "reactive derivative" of the carboxylic acid represented by the above formula (III) mean a carboxylic acid derivative, for example, an acid halide, an acid anhydride or a mixed acid anhydride usually used in the synthetic organic chemistry field and having high reactivity.

[0101] The reaction can more smoothly be made to proceed by suitably using an adequate amount of a dehydrating agent such as molecular sieve; a coupling reagent such as dicyclohexylcarbodiimide (DCC), N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide (EDCI or WSC), carbonyldiimidazole (CDI), N-hydroxysuccinimide (HOSu), N-hydroxybenzotriazole (HOBt), benzotriazol-1-yloxytris(pyrrolidinol) phosphonium hexafluorophosphate (PyBOP), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-(5-norbornene-2,3-dicarboxyimide)-1,1,3,3-tetramethyluronium tetrafluorobonite (TNTU), O-(N-succinimidyl)-1,1,3,3-tetramethyluronium hexafluorophosphate (TSTU) or bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP); a base such as an inorganic base such as potassium carbonate, calcium carbonate or sodium hydrogencarbonate; amines such as triethylamine, diisoproylethylamine or pyridine or a polymer supported base such as (piperidinomethyl)polystyrene, (morpholinomethyl)polystyrene, (dimethylaminomethyl)polystyrene or poly(4-vinylpyridine).

(Preparation process 2)

[0102] A preparation process comprises reacting one equivalent of an alkylating reagent represented by the following formula (IV):

$$R^1$$
 \rightarrow (CH₂)_j -X (IV)

wherein R^1 , R^2 and j are each the same as defined in the above formula (I); X is a halogen atom, an alkylsulfonyloxy group or an arylsulfonyloxy group, with 0.1 to 10 equivalents of a compound represented by the following formula (V):=

$$\begin{array}{c} \begin{pmatrix} (CH_{2})_{k} \\ HN \\ (CH_{2})_{m} \end{pmatrix} - (CH_{2})_{n} - N - \overset{||}{C} - (CH_{2})_{p} - \overset{||}{C} + (CH_{2})_{q} - G - R^{6} \end{array}$$

$$(V)$$

wherein R³, R⁴, R⁵, R⁶, G, k, m, n, p and q are each the same as defined in the above formula (I), in the absence or presence of a solvent.

[0103] The reaction can more smoothly be made to proceed by suitably using a base similar to that in the preparation process 1. Furthermore, the reaction sometimes can be promoted by the presence of an iodide such as potassium iodide or sodium iodide.

[0104] In the above formula (IV), X is a halogen atom, an alkylsulfonyloxy group or an arylsulfonyloxy group. Examples of the halogen atom preferably include a chlorine atom, a bromine atom and an iodine atom. Specific examples of the alkylsulfonyloxy group preferably include a methylsulfonyloxy group, a trifluoromethylsulfonyloxy group and the like, and the specific example of the arylsulfonyloxy group preferably includes tosyloxy group.

(Preparation process 3)

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[0105] A preparation process comprises reacting one equivalent of an aldehyde represented by the following formula (VI):

$$\begin{array}{c}
R^{1} \\
 \longrightarrow (CH_{2})_{j-1} - CHO
\end{array} (VI)$$

wherein R¹ and R² are each the same as defined in the above formula (I); j is 1 or 2, or an aldehyde represented by the following formula (VII):

wherein R¹ is the same as defined for R¹ in the above formula (I); the compound corresponds to the case where j is 0, with 0.1 to 10 equivalents of a compound represented by the above formula (V) in the absence or presence of a solvent.
 [0106] The reaction is usually called a reductive amination reaction and a catalytic hydrogenation reaction using a catalyst containing a metal such as palladium, platinum, nickel or rhodium, a hydrogenation reaction using a complex hydride such as lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride and borane, an electrolytic reducing reaction or the like can be used as reductive conditions.

(Preparation process 4)

[0107] A preparation process comprises reacting one equivalent of a compound represented by the following formula (VIII):

wherein R¹, R², R³, R⁴, R⁵, R⁷, j, k, m, n, p and q are each the same as defined in the above formula (I), with 0.1 to 10 equivalents of a carboxylic acid or a sulfonic acid represented by the following formula (IX):

$$HO-A^-R^6$$
 (IX)

wherein R⁶ is the same as defined in the above formula (I); A is a carbonyl group or a sulfonyl group, or a reactive derivative thereof in the absence or presence of a solvent

[0108] The reactive derivative of the carboxylic acid or sulfonic acid represented by the above formula (IX) means a carboxylic acid derivative or sulfonic acid derivative, for example, an acid halide, an acid anhydride or a mixed acid anhydride usually used in the synthetic organic chemistry field and having high reactivity. The reaction can more smoothly be made to proceed by suitably using a dehydrating agent, a coupling reagent or a base similar to that in the above preparation process 1.

(Preparation process 5)

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[0109] A preparation process comprises reacting one equivalent of a compound represented by the above formula (VIII) with 0.1 to 10 equivalents of an isocyanate or an isothiocyanate represented by the following formula (X):

$$Z=C=N-R^{6}$$
 (X)

wherein R⁶ is the same as defined in the above formula (I); Z is an oxygen atom or a sulfur atom, in the absence or presence of a solvent.

(Preparation process 6)

[0110] A preparation process comprises reacting one equivalent of a compound represented by the following formula (XI):

wherein R¹, R², R³, R⁴, R⁵, j, k, m, n, p and q are each the same as defined in the above formula (I); A is a carbonyl group or a sulfonyl group,

with 0.1 to 10 equivalents of an amine represented by the following formula (XII):

$$R^6-NH_2$$
 (XII)

wherein R⁶ is the same as defined for R⁶ in the above formula (I), in the absence or presence of a solvent.

[0111] The reaction can more smoothly be made to proceed by suitably using a dehydrating agent, a coupling reagent or a base similar to that in the above preparation process 1.

[0112] In the above preparation processes 1 to 6, when a substrate used for each reaction has substitutents regarded as usually reacting under respective reaction conditions in the organic synthetic chemistry or having adverse effects on the reaction, the functional groups can be protected with a known suitable protecting group, and the substrate can be used for the reaction and then deprotected by a conventional known method to afford the objective compound.

[0113] In addition, the compounds used in the present invention can be obtained by further converting (single or plural) substituents of the compound produced by the above preparation process 1 - 6 using a known reaction usually used in the organic synthetic chemistry, for example, an alkylation reaction, an acylation reaction or a reduction reaction.

[0114] In the above respective preparation processes, a halogenated hydrocarbon such as dichloromethane or chloroform, an aromatic hydrocarbon such as benzene or toluene, ethers such as diethyl ether or tetrahydrofuran, esters such as ethyl acetate, an aprotic polar solvent such as dimethylformamide, dimethyl sulfoxide or acetonitrile and alcohols such as methanol, ethanol or isopropyl alcohol are suitably used as a reaction solvent according to the reaction.

such as ethyl acetate, an aprotic polar solvent such as dimethylformamide, dimethyl sulfoxide or acetonitrile and alcohols such as methanol, ethanol or isopropyl alcohol are suitably used as a reaction solvent according to the reaction. [0115] In each of the preparation processes, the reaction temperature is within the range of -78 to +150 °C, preferably within the range of 0 to 100°C. After completing the reaction, the objective cyclic amine compounds represented by the above formula (I) can be isolated by carrying out usual isolating and purifying operations, i.e., concentration, filteration, extraction, solid-phase extraction, recrystallization or chromatography. The compounds can be converted into their pharmaceutically acceptable acid addition salts thereof or their C_1 - C_6 alkyl addition salts thereof according to a usual method.

Examples

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[0116] The present invention is detailed specifically based on Examples; however, the present invention is not restricted to compounds described in the Examples. The Compound number (Compd. No.) assigned to each compound in the following Examples corresponds to the Compd. No. assigned to each compound cited as a preferred specific example in Tables 1.1 to 1.206.

[Reference Example 1] Synthesis of 3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride

[0117] 4-Chlorobenzyl chloride (4.15 g, 25.8 mmol) and $^{\rm i}$ Pr $_2$ NEt (6.67 g, 51.6 mmol) were added to a DMF (50 mL) solution of 3-[(tert-butoxycarbonyl)amino]pyrrolidine (4.81 g, 25.8 mmol). The reaction mixture was stirred at 70 °C for 15 hours, and the solvent was removed under reduced pressure. The objective 3-[(tert-butoxycarbonyl)amino]-1-(4-chlorobenzyl)pyrrolidine (6.43 g, 80%) was obtained as an off-white solid by recrystallization (acetonitrile, 50 mL). $^{\rm 1}$ H NMR (CDCl $_3$, 300MHz) δ 1.37 (s, 9 H), 1.5-1.7 (br, 1 H), 2.1-2.4 (m, 2 H), 2.5-2.7 (m, 2 H), 2.83 (br, 1 H), 3.57 (s, 2 H), 4.1-4.3 (br, 1 H), 4.9-5.1 (br, 1 H), 7.15-7.35 (br, 4 H); the purity was determined by RPLC/MS (98%). ESI/MS m/e 311.0 (M++H, C₁₆H $_{24}$ CIN $_2$ O $_2$).

[0118] To a methanol solution (80 mL) of the 3-[(tert-butoxycarbonyl)amino]-1-(4-chlorobenzyl)pyrrolidine (6.38 g, 20.5 mmol), was added 1 M HCI-Et₂O (100 mL). The resulting mixture was stirred at 25 °C for 15 hours. The solvent was removed under reduced pressure to provide a solid, which was purified by recrystallization (methanol/acetonitrile = 1:2, 130 mL) to thereby afford 3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride (4.939 g, 85%) as a white powder. 1 H NMR (d₆-DMSO, 300MHz) δ 3.15 (br, 1 H), 3.3-3.75 (br-m, 4 H), 3.9 (br, 1 H), 4.05 (br, 1 H), 4.44 (br, 1 H), 4.54 (br, 1 H), 7.5-7.7 (m, 4 H), 8.45 (br, 1 H), 8.60 (br, 1 H); the purity was determined by RPLC/MS (>99%). ESI/MS m/e 211.0 (M++H, C₁₁H₁₆ClN₂).

[0119] Optically active (R)-3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride and (S)-3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride were synthesized by using the respective corresponding starting materials according to the above method. The products exhibited the same ¹H NMR as that of the above racemate.

[Example 1] Synthesis of 3-(N-benzoylglycyl)amino-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 1)

[0120] N-Benzoylglycine (9.3 mg, 0.055 mmol), 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (ED-Cl) (1.05 mg) and 1-hydroxybenzotriazole hydrate (HOBt) (7.4 mg) were added to a chloroform (2.5 mL) solution of 3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride (14.2 mg, 0.050 mmol) and triethylamine (15.2 mg). The resulting reaction mixture was stirred at 25 °C for 16 hours and then washed with a 2 M aqueous solution of NaOH (2mL \times 2) and brine. After filtration through a PTFE membrane filter, the solvent was removed under reduced pressure to provide 3-(N-benzoylglycyl)amino-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 1) as an off-white oil (17.7 mg, 95%). The purity was determined by RPLC/MS (95%). ESI/MS mle 372.0 (M++H, $C_{20}H_{22}CIN_3O_2$).

[Examples 2 to 32]

[0121] The compounds used in the present invention were synthesized by using the respective corresponding starting

materials and reactants according to the method in Example 1. The data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 2.

Table 2

lable 2							
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)		
2	2	C ₂₁ H ₂₄ CIN ₃ O ₂	386	16.4	85		
3	3	C ₁₉ H ₂₁ CIN ₄ O ₂	373	18.7	100		
4	4	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₂	440	57.2	69		
5	82	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	454	5.6	11		
6	85	C ₂₁ H ₂₄ CIN ₃ O ₂	386	22.6	59		
7	86	C ₂₁ H ₂₃ CIN ₄ O ₄	431	21.2	98		
8	214	C ₂₂ H ₂₅ CIN ₂ O ₂	385	23.9	62		
9	215	C ₂₃ H ₂₇ CIN ₂ O ₃	415	17.4	84		
10	216	C ₂₀ H ₂₃ CIN ₂ O ₂ S	391	21.6	Q		
11	217	C ₂₃ H ₂₇ CIN ₂ O ₄	431	15.3	66		
12	218	C ₂₃ H ₂₇ CIN ₂ O ₂	399	12.8	64		
13	219	C ₂₂ H ₂₄ CIFN ₂ O ₃	419	18.1	86		
14	220	C ₂₂ H ₂₅ CIN ₂ O ₂	385	16.4	85		
15	- 221	C ₂₁ H ₂₃ CIN ₂ O ₂	371	14.9	80		
16	222	C ₂₁ H ₂₂ Cl ₂ N ₂ O ₂	405	13.3	65		
17	223	C ₂₅ H ₃₁ CIN ₂ O ₃	443	18.4*	63		
18	224	C ₂₀ H ₂₃ CIN ₂ O ₃ S	407	11.2	28		
19	225	C ₂₂ H ₂₆ CIN ₃ O ₂	400	22,7	Q		
20	226	C ₂₃ H ₂₈ CIN ₃ O ₃	430	21.0	98		
21	227	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₂	434	21.9	100		
22	228	C ₂₃ H ₂₈ CIN ₃ O ₃	430	20.8	97		
23	229	C ₂₅ H ₃₂ CIN ₃ O ₂	462	25.4	Q		
24	230	C ₂₆ H ₃₁ CIFN ₃ O ₂	472	26.0	Q		
25	231	C ₂₄ H ₂₈ CIN ₃ O ₃	442	30.3*	a		
26	232	C ₂₂ H ₃₂ CIN ₃ O ₂	406	3.9	19		
27	233	C ₂₃ H ₂₈ CIN ₃ O ₂	414	8.5	41		
28	234	C ₂₂ H ₂₇ CIN ₄ O ₂	415	7.3	35		
29	235	C ₂₄ H ₂₉ Cl ₂ N ₃ O ₂	462	9.0	39		
30	236	C ₂₅ H ₂₉ CIN ₄ O ₃ S	501	17.4	69		
31	237	C ₂₁ H ₂₄ CIN ₃ O ₃	402	14.2	71		
32	238	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₃	436	23.4	Q		
	•	eld (mg) of trifluoroace	tate".				
Q mea	Q means "Quantitative".						

[Reference Example 2] Synthesis of (R)-3-[(N-tert -butoxycarbonyl)glycyl]amino-1-(4 chlorobenyl)pyrrolidine

[0122] A mixture of (R)-3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride (4.54 g, 16.0 mmol) with a 2 M solution (80 mL) of NaOH and ethyl acetate (80 mL) was stirred, and the organic layer was separated to extract the aqueous

layer with ethyl acetate (80 mL×2). The organic layers were combined, dried over anhydrous sodium sulfate, then filtered and concentrated to thereby afford free (R)-3-amino-1-(4-chlorobenzyl)pyrrolidine (3.35 g, 99%).

[0123] To a dichloromethane (80 mL) solution of the (R)-3-amino-1-(4-chlorobenzyl)pyrrolidine (3.35 g, 16 mmol), were added triethylamine (2.5 mL, 17.6 mmol), N-tert-butoxycarbonylglycine (2.79 g, 16.0 mmol), EDCI (3.07 g, 16.0 mmol) and HOBt (12.16 g, 16 mmol). The resulting reaction mixture was stirred at 25 °C for 16 hours, and a 2 M solution (80 mL) of NaOH was then added thereto. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (100 mL \times 3). The organic layers were combined, washed with water (100 mL \times 2) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography (SiO₂, ethyl acetate) to thereby provide the objective (R)-3- [N-(tert-butoxycarbonyl)glycyl]amino-1-(4-chlorobenzyl)pyrrolidine (5.40 g, 92%).

[Reference Example 3] Synthesis of (R)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine

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[0124] A 4 M HCl dioxane (38 mL) solution was added to a methanol (60 mL) solution of (R)-3-[N-(tert-butoxycarbonyl) glycyl]amino-1-(4-chlorobenzyl)pyrrolidine (5.39 g, 14.7 mmol). The resulting solution was stirred at room temperature for 2 hours. The reaction mixture was concentrated, and a 2 M solution (80 mL) of NaOH was added. The mixture solution was extracted with dichloromethane (80 mL \times 3), and the extracts were combined, dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (SiO₂, ethyl acetate/ethanol/triethylamine = 90:5:5) to afford (R)-3-(glycylamino)-1-(4-chlorobenzyl)pyrrolidine (3.374 g, 86%) ¹H NMR (CDCl₃, 270MHz) δ 1.77 (dd, J = 1.3 and 6.9 Hz, 1 H), 2.20-3.39 (m, 2 H), 2.53 (dd, J = 3.3 and 9.6 Hz, 1 H), 2.62 (dd, J = 6.6 and 9.6 Hz, 1 H), 2.78-2.87 (m, 1 H), 3.31 (s, 2 H), 3.57(s, 2 H), 4.38-4.53 (br, 1 H), 7.18-7.32 (m, 4 H), 7.39(br, s, 1 H).

[0125] Other 3-acylamino-1-(4-chlorobenzyl)pyrrolidines were synthesized by using the respective corresponding starting materials and reactants according to the methods of Reference Examples 2 and 3.

- (S)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine: 3.45 g, 79% (two steps).
- (R)-3-(β-alanylamino)-1-(4-chlorobenzyl)pyrrolidine: 3.79 g, 85% (two steps).
- (S)-3-(β-alanylamino)-1-(4-chlorobenzyl)pyrrolidine: 3.72 g, 86% (two steps)
- (R)-3-[(S)-alanylamino]-1-(4-chlorobenzyl)pyrrolidine: 368 mg, 65% (two steps).
- (R)-3-[(R)-alanylamino]-1-(4-chlorobenzyl)pyrrolidine: 425 mg, 75% (two steps).
- (R)-3-[(2S)-2-amino-3-thienylpropanoyl]amino-1-(4-chlorobenzyl)pyrrolidine: 566 mg, 78% (two step).
- (R)-3-[(2R)-2-amino-3-thienylpropanoyl]amino-1-(4-chlorobenzyl)pyrrolidine: 5.85 mg, 81% (two steps).
- (R)-3-(2-amino-2-methylpropanoyl)amino-1-(4-chlorobenzyl)pyrrolidine: 404 mg, 66% (two steps).
- (R)-3-[(2S)-2-amino-4-(methylsulfonyl)butanoyl]amino-1-(4-chlorobenzyl)pyrrolidine: 535 mg, 72% (two steps).
- [0126] Furthermore, (R)-3-(glycylamino)-1-(4-methylbenzyl)pyrrolidine, (R)-1-(4-bromobenzyl)-3-(glycylamino)pyrrolidine, (R)-1-(2,4-dimethylbenzyl)-3-(glycylamino)pyrrolidine and (R)-1-(3,5-dimethylisoxazol-4-ylmethyl)-3-(glycylamino)pyrrolidine were synthesized by using the respective corresponding starting materials and reactants according to the methods of Reference Examples 1, 2 and 3.
 - [0127] (R)-3-(glycylamino)-1-(4-methylbenzyl)pyrrolidine: 4.65 g, yield 62% (yield from 3-[(tert-butoxycarbonyl)amino]pyrrolidine).
 - [0128] (R)-1-(4-bromobenzyl)-3-(glycylamino)pyrrolidine: 2.55 g, yield 68% (yield from (R)-3-amino-1-(4-bromobenzyl)pyrrolidine); 1 H NMR (CDCl $_{3}$ 270MHz) δ 1.37-1.78 (m, 3 H), 2.23-2.39 (m, 2 H), 2.50-2.67 (m, 2 H), 2.80-2.89 (m, 1 H), 3.32 (s, 2 H), 4.39-4.55 (m, 1 H), 7.21 (d, J = 6.5 Hz, 2 H), 7.45 (d, J = 6.5 Hz, 2 H).
 - [0129] (R)-1-(2,4-dimethylbenzyl)-3-(glycylamino)pyrrolidine: 1.56 g, yield 58% (yield from 3-[(tert-butroxycarbonyl) amino]pyrrolidine); 1 H NMR (CDCl₃, 270MHz) δ 1.55-1.78 (m, 3 H), 2.30 (s, 3 H), 2.23-2.31 (m, 2 H), 2.33 (s, 3 H), 2.51-2.63 (m, 2 H), 2.78-2.87 (m, 1 H), 3.30 (s, 2 H), 3.55 (s, 2 H), 4.38-4.60 (m, 1 H), 6.95 (d, J = 7.6 Hz, 1 H), 6.97 (s, 1 H), 7.13 (d, J = 7.6 Hz, 1 H), 7.43 (br-s, 1 H).
 - [0130] (R)-1-(3,5-dimethylisoxazol-4-ylmethyl)-3-(glycylamino)pyrrolidine: 3.14 g, yield 45% (yield from 3-[(tert-butoxycarbonyl)amino]pyrrolidine).

[Example 33] Synthesis of (S)-3-[N-[3,5-bis(trifluoromethyl)benzoyl]glycyl]amino-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 5).

[0131] A chloroform solution (0.4 mL) of. 3,5-bis(trifluoromethyl)benzoyl chloride (0.060 mmol) was added to a chloroform (1.0 mL) solution of (S)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (0.050 mmol) and triethylamine (0.070 mmol). The resulting reaction mixture was stirred at room temperature for 2.5 hours, and an (aminomethyl)polystyrene resin (1.04 mmol/g, 50 mg, 50 mmol) was then added. The prepared mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered, and the resin was washed with dichloromethane (0.5 mL). The filtrate and

the washing were combined, and dichloromethane (4 mL) was added. The resulting solution was washed with a 2 M aqueous solution (0.5 mL) of NaOH and concentrated to thereby provide (S)-3-[N-[3,5-bis(trifluoromethyl)benzoyl]glycyl]amino-1-(4-chlorobenzyl)pyrrolidine. (Compd. No. 5) (14.4 mg, 57%). The purity was determined by RPLC/MS (97%). ESI/MS m/e 508.0 (M++H, $C_{22}H_{20}CIF_6N_3O_2$).

[Examples 34 to 239]

[0132] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 33. Data of ESI/MS, yields (mg) and yields (%) are collectively shown on Table 3.

Table 3

Table 3							
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)		
34	- 5	C ₂₂ H ₂₀ ClF ₆ N ₃ O ₂	508.0	14.4	57		
35	6	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₂	440.0	17.0	77		
36	7	C ₂₀ H ₂₁ BrClN ₃ O ₂	450.0	17.7	79		
37	8	C ₂₀ H ₂₁ CIFN ₃ O ₂	390.0	12.7	65		
38	9	C ₂₀ H ₂₀ Cl ₃ N ₃ O ₂	440.0	39.0	Q		
39	10	C ₂₁ H ₂₄ CIN ₃ O ₃	402.5	23.5	Q		
40	11	C ₂₂ H ₂₆ CIN ₃ O ₄	432.5	22.4	Q		
41	12	C ₂₂ H ₂₆ CIN ₃ O ₄	432.5	15.9	74		
42	13	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₂	440.0	13.1	60		
43	14	C ₂₁ H ₂₄ CIN ₃ O ₂	386.0	16.4	85		
44	15	C ₂₀ H ₂₁ Cl ₂ N ₃ O ₂	406.0	15.7	77		
45	16	C ₂₁ H ₂₄ CIN ₃ O ₂	402.0	28.2	Q		
46	17 .	C ₂₀ H ₂₀ Cl ₃ N ₃ O ₂	442.0	35.6	Q		
47	18	C ₂₁ H ₂₁ CIN ₄ O ₂	397:5	22.8	Q		
48	19	C ₂₁ H ₂₂ CIN ₃ O ₄	416.0	16.3	78		
49	20	C ₂₁ H ₂₀ CIF ₄ N ₃ O ₂	458.0	24.9	Q		
50	21	C ₂₁ H ₂₀ ClF ₄ N ₃ O ₂	458.0	17.9	78		
51	22	C ₂₁ H ₂₀ CIF ₄ N ₃ O ₂	458.0	9.4	41		
52	23	C ₂₁ H ₂₀ CIF ₄ N ₃ O ₂	458.0	15.4	67		
53	24	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₃	456.0	20.7	91		
54	25	C ₂₁ H ₂₀ CIF ₄ N ₃ O ₂	458.0	18.5	81		
55	26	C ₂₀ H ₂₁ CIN ₄ O ₄	417.0	21.9	Q		
56	27	C ₂₀ H ₂₁ CIN ₄ O ₄	417.0	16.8	81		
57	28	C ₂₀ H ₂₁ CIN ₄ O ₄	417.0	6.8	33		
58	29	C ₂₂ H ₂₀ CIF ₆ N ₃ O ₂	508.0	20:8	82		
59	30	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₂	440.0	15.2	69		
60	31	C ₂₀ H ₂₁ BrClN ₃ O ₂	450.0	15.6	69		
61	32	C ₂₀ H ₂₁ CIFN ₃ O ₂	390.0	11.8	61		
62	33	C ₂₀ H ₂₀ Cl ₃ N ₃ O ₂	440.0	15.8	72		
63	34	C ₂₁ H ₂₄ CIN ₃ O ₃	402.5	33.8	Q		

Table 3 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
64	35	C ₂₂ H ₂₆ CIN ₃ O ₄	432.5	56.1	Q
65	36	C ₂₂ H ₂₆ CIN ₃ O ₄	432.5	37.6	Q
66	37	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₂	440.0	12.6	57
67	38	C ₂₁ H ₂₄ CIN ₃ O ₂	386.0	12.3	64
68	39	C ₂₀ H ₂₁ Cl ₂ N ₃ O ₂	406.0	15.9	78
69	40	C ₂₁ H ₂₄ CIN ₃ O ₂	402.0	11.6	58
70	41	C ₂₀ H ₂₀ Cl ₃ N ₃ O ₂	442.0	17.8	81
71	42	C ₂₁ H ₂₁ CIN ₄ O ₂	397.5	22.4	Q
72	43	C ₂₁ H ₂₂ CIN ₃ O ₄	416.0	30.1	Q
73	44	C ₂₁ H ₂₀ CIF ₄ N ₃ O ₂	458.0	13.4	59
74	45	C ₂₁ H ₂₀ CIF ₄ N ₃ O ₂	458.0	13.2	58
75	46	C ₂₁ H ₂₀ CIF ₄ N ₃ O ₂	458.0	14.4	63
76	47	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₃	456.0	16.4	72
77	48	C ₂₁ H ₂₀ CIF ₄ N ₃ O ₂	458	16.5	72
78	49	C ₂₀ H ₂₁ CIN ₄ O ₄	417.0	12.5	60
79	50	C ₂₁ H ₂₀ CIF ₄ N ₃ O ₂	458.0	26.3	Q
80	51	C ₂₀ H ₂₁ BrClN ₃ O ₂	450.0	8.6	38
81	52	C ₂₀ H ₂₁ CIFN ₃ O ₂	390.5	4.1	21
82	53	C ₂₀ H ₂₁ Cl ₂ N ₃ O ₂	406.0	5.4	27
83	54	C ₂₀ H ₂₀ Cl ₃ N ₃ O ₂	440.0	8.8	40
84	55	C ₂₀ H ₂₀ BrCl ₄ N ₃ O ₂	440.0	7.7	35
85	56	C ₂₁ H ₂₄ CIN ₃ O ₂	386.0	4.8	25
86	57	C ₂₂ H ₂₆ CIN ₃ O ₄	429.5	4.9	23
87	58	C ₂₀ H ₂₁ Cl ₂ N ₃ O ₂	406.0	4.1	20
88	59	C ₂₀ H ₂₁ BrClN ₃ O ₂	452.0	3.5	16
89	60	C ₂₆ H ₂₆ CIN ₃ O ₂	448.5	7.3	33
90	61	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₂	440.0	7.1	32
91	62	C ₂₁ H ₂₄ CIN ₃ O ₂	386.0	10.4	54
92	63	C ₂₂ H ₂₆ CIN ₃ O ₂	400.5	6.0	30
93	64	C ₂₁ H ₂₁ CIN ₄ O ₂	397.0	7.0	35
94	65	C ₂₄ H ₂₄ CIN ₃ O ₂	422.0	7.7	36
95	66	C ₂₄ H ₂₄ CIN ₃ O ₂	422.0	6.3	30
· 96	67	C ₂₀ H ₂₀ CIF ₂ N ₃ O ₂	408.0	4.7	23
97	68	C ₂₀ H ₂₀ CIF ₂ N ₃ O ₂	408.0	7.8	38
98	69	C ₂₀ H ₂₀ CIF ₂ N ₃ O ₂	408.0	7.3	36
99	70	C ₂₀ H ₂₀ CIF ₂ N ₃ O ₂	408.0	9.1	45
100	71	C ₂₂ H ₂₆ CIN ₃ O ₄	429.0	5.6	26
101	72	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₂	456.0	6.2	27

Table 3 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
102	73	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₂	456.5	16.8	74
103	74	C ₂₂ H ₂₄ CIN ₃ O ₄	430.0	16.4	76
104	75	C ₂₁ H ₂₀ CIF ₄ N ₃ O ₂	458.0	16.1	70
105	76	C ₂₁ H ₂₀ ClF ₄ N ₃ O ₂	458.0	17.0	74 -
106	77	C ₂₀ H ₁₉ CIF ₃ N ₃ O ₂	426.0	. 16.2	76
107	78	C ₂₀ H ₁₉ CIF ₃ N ₃ O ₂	426.0	18.0	85
108	79	C ₂₂ H ₂₀ CIF ₆ N ₃ O ₂	508.0	18.8	74
109	80	C ₂₂ H ₂₀ CIF ₆ N ₃ O ₂	508.0	16.4	65
110	81	C ₂₂ H ₂₆ CIN ₃ O ₂	400.0	13.9	70
111	83	C ₂₀ H ₂₁ CIN ₄ O ₄	417.0	16.0	77
112	84	C ₂₀ H ₂₁ CIN ₄ O ₄	417.0	21.6	Q
113	87	C ₂₃ H ₂₂ CIF ₆ N ₃ O ₂	522.0	17.5	67
114	88	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	454.0	13.9	61
115	89	C ₂₁ H ₂₃ BrClN ₃ O ₂	466.0	15.4	66
116	. 90	C ₂₁ H ₂₃ CIFN ₃ O ₂	404.0	10.7	53
117	91	C ₂₁ H ₂₂ Cl ₃ N ₃ O ₂	456.0	13.7	60
118	92	C ₂₂ H ₂₆ ClN ₃ O ₃	416.0	38.4	Q
119	93	C ₂₃ H ₂₈ ClN ₃ O ₄	446.0	25.2	Q
120	94	C ₂₃ H ₂₈ ClN ₃ O ₄	446.0	16.5	. 74
121	95	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	454.0	16.3	72
122	96	C ₂₂ H ₂₆ CIN ₃ O ₂	400.5	16.7	84
123	97	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	11.2	53
124	98	C ₂₂ H ₂₆ CIN ₃ O ₂	416.5	11.8	57
125	99	C ₂₁ H ₂₂ Cl ₃ N ₃ O ₂	454.0	14.8	65
126	100	C ₂₂ H ₂₃ CIN ₄ O ₂	411.0	9.5	46
127	101	C ₂₂ H ₂₄ CIN ₃ O ₄	430.5	13.2	61
128	102	C ₂₂ H ₂₂ CIF ₄ N ₃ O ₂	472.0	13.1	56
129	103	C ₂₂ H ₂₂ CIF ₄ N ₃ O ₂	472.0	36.5	Q
130	104	C ₂₂ H ₂₂ CIF ₄ N ₃ O ₂	472.0	22.8	97
131	105	C ₂₂ H ₂₂ CIF ₄ N ₃ O ₂	472.0	20.1	85
132	106	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₃	470.0	27.4	Q
133	107	C ₂₂ H ₂₂ CIF ₄ N ₃ O ₂	472.0	18.5	78
134	108	C ₂₁ H ₂₃ CIN ₄ O ₄	431.0	11.9	55
135	109	C ₂₁ H ₂₃ CIN ₄ O ₄	431.0	23.9	Q
136	110	C ₂₁ H ₂₃ CIN ₄ O ₄	431.0	24.4	Q
137	111	C ₂₃ H ₂₂ CIF ₆ N ₃ O ₂	522.0	9.5	36
138	112	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	454.0	3.9	17
139	113	C ₂₁ H ₂₃ BrClN ₃ O ₂	466.0	7.5	32

Table 3 (continued)

		Table 6 (conti			
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
140	114	C ₂₁ H ₂₃ CIFN ₃ O ₂	404.0	6.1	30
141	115	C ₂₁ H ₂₂ Cl ₃ N ₃ O ₂	456.0	6.6	29
142	116	C ₂₂ H ₂₆ ClN ₃ O ₃	416.0	4.8	23
143	117	C ₂₃ H ₂₈ CIN ₃ O ₄	446.0	6.4	29
144	118	C ₂₃ H ₂₈ CIN ₃ O ₄	446.0	24.6	Q
145	119	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	454.0	5.2	23
146	120	C ₂₂ H ₂₆ CIN ₃ O ₂	400.5	4.4	22
147	121	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	7.8	37
148	122	C ₂₂ H ₂₆ CIN ₃ O ₂	416.5	14.1	68
149	123	C ₂₁ H ₂₂ Cl ₃ N ₃ O ₂	454.0	5.4	24
150	124	C ₂₂ H ₂₃ CIN ₄ O ₂	411.0	34.0	Q
151	125	C ₂₂ H ₂₄ CIN ₃ O ₄	430.5	32.0	Q
152	126	C ₂₂ H ₂₂ CIF ₄ N ₃ O ₂	472.0	4.6	19
153	127	C ₂₂ H ₂₂ CIF ₄ N ₃ O ₂	472.0	10.4	44
154	128	C ₂₂ H ₂₂ CIF ₄ N ₃ O ₂	472.0	7.3	31
155	129	C ₂₂ H ₂₂ CIF ₄ N ₃ O ₂	472.0	13.5	57
156	130	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₃	470.0	15.1	64
157	131	C ₂₂ H ₂₂ CIF ₄ N ₃ O ₂	472.0	8.6	36
158	132	C ₂₁ H ₂₃ CIN ₄ O ₄	431.0	4.4	20
159	133	C ₂₁ H ₂₃ CIN ₄ O ₄	431.0	32.0	Q
160	134	C ₂₁ H ₂₃ CIN ₄ O ₄	431.0	6.9	32
161	135	C ₂₁ H ₂₃ BrClN ₃ O ₂	466.0	7.8	34
162	- 136	C ₂₁ H ₂₃ CIFN ₃ O ₂	404.0	13.7	68
163	137	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.5	14.6	69
164	138	C ₂₁ H ₂₂ Cl ₃ N ₃ O ₂	454.0	17.7	78
165	139	C ₂₁ H ₂₂ BrCl ₄ N ₃ O ₂	454.0	17.2	76
166	140	C ₂₂ H ₂₆ CIN ₃ O ₂	400.0	15.0	75
167	141	C ₂₃ H ₂₈ CIN ₃ O ₄	443.5	13.9	62
168	142	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	13.7	65
169	143	C ₂₁ H ₂₃ BrClN ₃ O ₂	464.0	16.1	69
170	144	C ₂₇ H ₂₈ CIN ₃ O ₂	462.0	17.6	76
171	145	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	454.0	16.0	71
172	146	C ₂₂ H ₂₆ CIN ₃ O ₂	400.0	14.9	75
173	147	C ₂₃ H ₂₈ CIN ₃ O ₂	414.0	16.2	78
174	148	C ₂₂ H ₂₃ CIN ₄ O ₂	411.0	14.9	73
175	149	C ₂₅ H ₂₆ CIN ₃ O ₂	436.0	17.1	78
176	150	C ₂₅ H ₂₆ CIN ₃ O ₂	436.0	13.1	60
177	151	C ₂₁ H ₂₂ CIF ₂ N ₃ O ₂	422.0	14.8	70

Table 3 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
178	152	C ₂₁ H ₂₂ CIF ₂ N ₃ O ₂	422.0	15.3	73
179	153	C ₂₁ H ₂₂ CIF ₂ N ₃ O ₂	422.0	15.3	73
180	154	C ₂₁ H ₂₂ CIF ₂ N ₃ O ₂	422.0	16.4	78
181	155	C ₂₃ H ₂₈ CIN ₃ O ₄	443.0	16.9	76
182	156	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	470.5	12.6	54
183	157	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	470.0	20.0	85
184	158	C ₂₃ H ₂₆ CiN ₃ O ₄	444.0	17.4	78
185	159	C ₂₂ H ₂₂ CIF ₄ N ₃ O ₂	472.0	18.4	78
186	160	C ₂₂ H ₂₂ CIF ₄ N ₃ O ₂	472.0	19.6	83
187	161	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₂	440.0	17.0	77
188	162	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₂	440.0	17.1	78
189	163	C ₂₃ H ₂₂ CIF ₆ N ₃ O ₂	522.0	20.8	80
190	164	C ₂₃ H ₂₂ CIF ₆ N ₃ O ₂	522.0	2.7	10
191	165	C ₂₃ H ₂₈ CIN ₃ O ₂	414.0	16.4	79
192	166	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	454.0	8.6	38
193	167	C ₂₁ H ₂₃ BrClN ₃ O ₂	464.0	11.6	50
194	168	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	11.5	55
195	169	C ₂₁ H ₂₂ Cl ₃ N ₃ O ₂	454.0	10.0	44
196	170	C ₂₂ H ₂₂ CIF ₄ N ₃ O ₂	472.0	10.4	44
197	171	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	8.9	42
198	172	C ₂₁ H ₂₄ CIN ₃ O ₂	386.0	10.3	53
199	173	C ₂₁ H ₂₃ CIN ₄ O ₄	431.0	14.6	68
200	174	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	454.0	10.4	46
201	175	C ₂₁ H ₂₃ BrClN ₃ O ₂	464.0	13.4	58
202	176	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	12.7	60
203	177	C ₂₁ H ₂₂ Cl ₃ N ₃ O ₂	454.0	13.2	58
204	178	C ₂₂ H ₂₂ CIF ₄ N ₃ O ₂	472.0	12.9	55
205	179	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	13.3	63
206	180	C ₂₁ H ₂₄ CIN ₃ O ₂	386.0	24.2	Q
207	181	C ₂₁ H ₂₃ CIN ₄ O ₄	431.0	1.0	1
208	182	C ₂₃ H ₂₅ CIF ₃ N ₃ O ₂	468.0	15.1	65
209	183	C ₂₂ H ₂₅ BrClN ₃ O ₂	478.0	18.0	75
210	184	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₂	434.0	16,3	75
211	185	C ₂₂ H ₂₄ Cl ₃ N ₃ O ₂	468.0	18.6	79
212	186	C ₂₃ H ₂₄ CIF ₄ N ₃ O ₂	486.0	16.5	68
213	187	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₂	434.0	14.4	66
214	188	C ₂₂ H ₂₆ CIN ₃ O ₂	400.0	14.0	70
215	189	C ₂₂ H ₂₅ CIN ₄ O ₄	445.0	16.8	76

Table 3 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
216	190	C ₂₆ H ₂₅ CIF ₃ N ₃ O ₂ S	536.0	17.7	66
217	191	C ₂₅ H ₂₅ BrClN ₃ O ₂ S	546.0	20.4	75
218	192	C ₂₅ H ₂₅ Cl ₂ N ₃ O ₂ S	502.0	16.9	67
219	193	C ₂₅ H ₂₄ Cl ₃ N ₃ O ₂ S	536.0	18.3	68
220	194	C ₂₆ H ₂₄ CIF ₄ N ₃ O ₂ S	554.0	19.4	70
221	195	C ₂₅ H ₂₅ Cl ₂ N ₃ O ₂ S	502.0	19.1	76
222	196	C ₂₅ H ₂₆ CIN ₃ O ₂ S	468.0	16.0	68
223	197	C ₂₅ H ₂₅ CIN ₄ O ₄ S	513.0	18.4	72
224	198	C ₂₆ H ₂₅ CIF ₃ N ₃ O ₂ S	536.0	13.9	52
225	199	C ₂₅ H ₂₅ BrClN ₃ O ₂ S	546.0	12.9	47
226	200	C ₂₅ H ₂₅ Cl ₂ N ₃ O ₂ S	502.0	15.6	62
227	201	C ₂₅ H ₂₄ Cl ₃ N ₃ O ₂ S	536.0	17.3	64
228	202	C ₂₆ H ₂₄ CIF ₄ N ₃ O ₂ S	554.0	15.4	56
229	203	C ₂₅ H ₂₅ Cl ₂ N ₃ O ₂ S	502.0	13.5	54
230	204	C ₂₅ H ₂₆ CIN ₃ O ₂ S	468.0	13.7	59
231	205	C ₂₅ H ₂₅ CIN ₄ O ₄ S	513.0	13.9	54
232	206	C ₂₄ H ₂₇ CIF ₃ N ₃ O ₄ S	546.0	10.0	37
233	207	C ₂₃ H ₂₇ BrClN ₃ O ₄ S	558.0	17.1	61
234	208	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₄ S	512.0	17.0	66
235	209	C ₂₃ H ₂₆ Cl ₃ N ₃ O ₄ S	546.0	7.3	27
236	210	C ₂₄ H ₂₆ CIF ₄ N ₃ O ₄ S	564.0	19.2	68
237	211	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₄ S	512.0	7.9	31
238	212	C ₂₃ H ₂₈ CIN ₃ O ₄ S	478.0	13.7	57
239	213	C ₂₃ H ₂₇ CIN ₄ O ₄ S	523.0	5.5	21
Note:	Q means "Quar	ntitative".			

[Example 240] Synthesis of (R)-3- [N-(3-fluoro-5-(trifluoromethyl)benzoyl]glycyl]amino-1-(3,5-dimethylisoxazol-4-ylmethyl)pyrrolidine (Compd. No. 1191)

[0133] A dichloromethane solution (1 mL) of 3-fluoro-5-(trifluoromethyl)benzoyl chloride (0.058 mmol) was added to a solution of (R)-1-(3,5-dimethylisoxazol-4-ylmethyl)-3-(glycylamino)pyrrolidine (0.050 mmol) and a piperidinomethyl-polystyrene (58 mg) in chloroform (0.2 mL) and dichloromethane (0.75 ml). The reaction mixture was stirred at room temperature for 2 hours, and methanol (1.0 mL) was then added. The resulting mixture was stirred at room temperature for 10 hours. The reaction mixture was loaded onto a Varian™ SCX column and washed with methanol (16 mL). The obtained crude product was eluted with a solution of 2 M NH₃ in methanol (6 mL) and concentrated to provide (R)-3-[N-[3-fluoro-5-(trifluoromethyl)benzoyl]glycyl]amino-1-(3,5-dimethylisoxazol-4-ylmethyl)pyrrolidine (Compd. No. 1191) (19.5 mg, 88%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 443.2 (M++H, C₂₀H₂₂F₄N₄O₃).

[Examples 241 to 265]

[0134] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 240. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 4.

Table 4

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
241	1192		443.2	19.2	87
		C ₂₀ H ₂₂ F ₄ N ₄ O ₃			
242	1193	C ₂₀ H ₂₃ F ₃ N ₄ O ₄	441.0	17.5	79
243	1194	C ₂₁ H ₂₂ F ₆ N ₄ O ₃	493.0	20.4	83
244	1195	C ₁₉ H ₂₃ BrN ₄ O ₃	435.1	16.8	77
245	1196	C ₁₉ H ₂₃ N ₅ O ₅	402.2	16.2	81
246	1197	C ₂₀ H ₂₂ F ₄ N ₄ O ₃	443.2	17.6	80
247	1198	C ₁₉ H ₂₃ CIN ₄ O ₃	391.0	16.5	84
248	1199	C ₂₀ H ₂₆ N ₄ O ₃	371.0	16.1	87
249	1200	C ₁₉ H ₂₂ Cl ₂ N ₄ O ₃	425.0	18.0	85
250	1201	C ₁₉ H ₂₂ F ₂ N ₄ O ₃	393.0	16.6	85
251	1202	C ₂₀ H ₂₂ F ₄ N ₄ O ₃	443.2	16.8	76
252	1203	C ₂₂ H ₂₄ F ₃ N ₃ O ₃	436.2	17.1	79
253	1204	C ₂₃ H ₂₃ F ₆ N ₃ O ₂	488.2	18.1	74
254	1205	C ₂₁ H ₂₄ BrN ₃ O ₂	430.0	17.5	81
255	1206	C ₂₁ H ₂₄ N ₄ O ₄	397.0	16.2	82
256	1207	C ₂₂ H ₂₃ F ₄ N ₃ O ₂	438.2	17.5	80
257	1208	C ₂₁ H ₂₄ CIN ₃ O ₂	386.0	15.8	82
258	1209	C ₂₂ H ₂₇ N ₃ O ₂	366.0	15.7	86
259	1210	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	17.8	85
260	1211	C ₂₁ H ₂₃ F ₂ N ₃ O ₂	388.0	16.3	84
261	1212	C ₂₂ H ₂₃ F ₄ N ₃ O ₂	438.2	17.4	80
262	1213	C ₂₄ H ₂₄ CIF ₆ N ₃ O ₂	536.2	24.0	90
263	1214	C ₂₃ H ₂₄ CIF ₄ N ₃ O ₃	486.2	22.2	91
264	1215	C ₂₂ H ₂₄ Cl ₃ N ₃ O ₂	467.9	20.9	89
265	1216	C ₂₂ H ₂₄ CIF ₂ N ₃ O ₂	436.0	19.3	89

[Example 266] Synthesis of (R)-1-(4-chlorobenzyl)-3-[[N-(4-dimethylaminobenzoyl)glycyl]amino]pyrrolidine (Compd. No. 952)

[0135] Triethylamine (0.021 mL, 0.15 mmol), 4-(dimethylamino)benzoic acid (10 mg, 0.061 mmol), EDCI (10.2 mg, 0.053 mmol) and HOBt (7.5 mg, 0.055 mmol) were added to a chloroform (2 mL) solution of (R)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (13.8 mg, 0.052 mmol). The resulting reaction mixture was stirred at room temperature for 15 hours. The solution was washed with a 2 M aqueous solution of NaOH (2 mL×2) and brine (2 mL), filtered through a PTFE membrane by using dichloromethane (3 mL), dried and concentrated to thereby afford (R)-1-(4-chlorobenzyl)-3-[[N-(4-dimethylaminobenzoyl)glycyl]amino]pyrrolidine (Compd. No. 952) (24.9 mg). The purity was determined by RPLC/MS (91%). ESI/MS m/e 415.0 (M++H, C₂₂H₂₇CIN₄O₂).

[Examples 267 to 347]

[0136] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 266. The obtained products, if necessary, were purified by solid-phase extraction (Varian™ SCX column) or chromatography (HPLC-C₁₈) to provide the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 5.

Table 5

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
267	951	C ₂₂ H ₂₄ CIN ₃ O ₄	430.0	26.3	Q
268	953	C ₂₃ H ₂₉ CIN ₄ O ₂	429.0	28.8	Q
269	954	C ₂₁ H ₂₅ CIN ₄ O ₂	401.0	27.9	Q
270	955	C ₂₂ H ₂₇ CIN ₄ O ₂	415.0	26.8	Q
271	956		402.0	10.3	51
271	957	C ₂₁ H ₂₄ ClN ₃ O ₃	388.0	1.4	7
		C ₂₀ H ₂₂ CIN ₃ O ₃		4	
273	958	C ₂₁ H ₂₄ CIN ₃ O ₃	402.5	1.2	6
274	959	C ₂₂ H ₂₅ CIN ₄ O ₃	429.5	4.7	22
275	960	C ₂₃ H ₂₇ CIN ₄ O ₃	443.0	10.9	49
276	961	C ₂₁ H ₂₅ CIN ₄ O ₂	401.0	28.4	Q
277	962	C ₂₂ H ₂₇ CIN ₄ O ₂	415.0	24.9	Q
278	963	C ₂₁ H ₂₄ CIN ₃ O ₃	402.0	4.4	22
279	964	C ₂₂ H ₂₄ CIN ₃ O ₄	430.0	29.5	Q
280	965	C ₂₃ H ₂₆ CIN ₃ O ₄	444.0	27.2	Q
281	966	C ₂₂ H ₂₄ CIN ₃ O ₃	414.0	27.0	Q
282	967	C ₂₃ H ₂₆ CIN ₃ O ₃	428.0	27.0	Q
283	968	C ₂₂ H ₂₃ CIN ₄ O ₂	411.0	21.4	Q
284	. 969	C ₂₃ H ₂₅ CIN ₄ O ₂	425.0	27.6	Q
285	970	C ₂₂ H ₂₇ CIN ₄ O ₂	415.0	28.6	Q
286	971	C ₂₃ H ₂₉ CIN ₄ O ₂	429.0	27.9	Q
287	972	C ₂₀ H ₂₃ CIN ₄ O ₂	387.0	26.2	Q
288	973	C ₂₁ H ₂₅ CIN ₄ O ₂	401.0	26.8	Q
289	974	C ₂₀ H ₂₃ CIN ₄ O ₂	387.0	26.6	Q
290	975	C ₂₁ H ₂₅ CIN ₄ O ₂	401.0	28.2	Q
291	976	C ₂₂ H ₂₃ CIN ₄ O ₂	411.0	29.2	Q
292	977	C ₂₃ H ₂₅ CIN ₄ O ₂	425.0	29.5	Q
293	978	C ₂₀ H ₂₁ CIN ₆ O ₂	413.0	2.2	11
294	979	C ₂₁ H ₂₃ CIN ₆ O ₂	427.0	10.2	48
295	980	C ₂₂ H ₂₅ CIN ₄ O ₃	429.0	28.8	Q
296	981	C ₂₃ H ₂₇ CIN ₄ O ₃	443.0	11.9	54
297	982	C ₂₂ H ₂₇ CIN ₄ O ₂	415.0	27.4	Q
298	983	C ₂₃ H ₂₉ CIN ₄ O ₂	429.5	28.1	Q
299	984	C ₂₁ H ₂₄ CIN ₃ O ₃	402.0	27.7	Q
300	985	C ₂₂ H ₂₆ CIN ₃ O ₃	416.0	28.6	Q
301	1149	C ₂₁ H ₂₈ N ₄ O ₄	401	15.5*	38
302	1150	C ₂₁ H ₂₈ N ₄ O ₃	385	10.9*	28
303	1151	C ₂₁ H ₂₅ F ₃ N ₄ O ₃	439	17.3*	39

Table 5 (continued)

	r	Table 5 (COIII			
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
304	1152	C ₂₁ H ₂₄ FN ₅ O ₃	415	12.7*	30
305	1153	C ₂₁ H ₂₄ CIN ₅ O ₃	430	17.5*	41
306	1154	C ₂₂ H ₂₇ N ₅ O ₃	410	20.6*	50
307	1155	C ₁₉ H ₂₃ F ₃ N ₄ O ₄	429	13.8*	32
308	1156	C ₂₁ H ₃₀ N ₄ O ₄	403	17.7*	43
309	1157	C ₁₈ H ₂₄ N ₄ O ₃ S ₂	409	12.6*	30
310	1158	C ₁₉ H ₂₃ Cl ₂ N ₅ O ₃	440	16.9*	38
311	1159	C ₂₂ H ₃₁ N ₅ O ₆	462	38.6*	85
312	1160	C ₂₀ H ₂₆ BrN ₅ O ₃	464	20.4	45
313	1289	C ₂₀ H ₂₇ N ₅ O ₄	403	5.8*	14
314	1290	C ₂₁ H ₂₉ N ₅ O ₃	400	6.9*	17
315	1291	C ₂₄ H ₂₈ N ₄ O ₂	405	22.4	68
316	1292	C ₂₂ H ₂₇ BrN ₄ O ₂	461	23.8	15
317	1293	C ₂₂ H ₂₃ F ₄ N ₃ O ₂	438	20.9	59
318	1294	C ₂₂ H ₂₃ F ₄ N ₃ O ₂	438	20.8	59
319	1295	C ₂₃ H ₃₁ N ₃ O ₃	398	17.5	54
320	1296	C ₂₀ H ₂₅ N ₃ O ₂ S ₂	404	18.8	58
321	1297	C ₂₁ H ₂₄ F ₃ N ₃ O ₃	424	18.1	53
322	1388	C ₂₁ H ₃₂ N ₆ O ₃	417	7.4*	24
323	1389	C ₁₉ H ₂₂ N ₆ O ₄	399	15.2	48
324	1401	C ₂₃ H ₂₅ CIN ₄ O ₂	425	8.3*	16
325	1402	C ₂₄ H ₃₂ N ₄ O ₅	457	8.3*	15
326	1403	C20H24N402	353	14.8	52
327	1404	C ₂₀ H ₂₄ N ₄ O ₂	353	17.0	60
328	1405	C ₂₁ H ₂₆ N ₄ O ₂ S	399	17.3	54
329	1407	C ₂₂ H ₂₈ N ₄ O ₂ S	413	19.1	57
330	1410	C ₁₉ H ₂₄ N ₄ O ₃	357	9.7*	59
331	1769	C ₂₂ H ₂₆ CIF ₃ N ₄ O ₅	519	11.6*	20
332	1770	C ₂₆ H ₂₈ Cl ₂ N ₆ O ₄	559	13.1*	21
333	1771	C ₂₆ H ₃₇ N ₅ O ₄	484	12.7*	23
334	1772	C ₂₈ H ₃₉ N ₅ O ₄	510	5.5*	9
335	1773	C ₂₈ H ₃₇ N ₅ O ₄	509	6.2*	11 -
336	1774	C ₂₈ H ₃₄ N ₆ O ₆	551	13.6*	22
337	2039	C ₁₉ H ₂₄ N ₄ O ₂	341	5.2*	14
338	2040	C ₂₂ H ₂₇ N ₃ O ₄	398	2.0* .	5
339	2041	C ₂₃ H ₂₉ N ₃ O ₃	396	6.2*	15
340	2042	C ₂₅ H ₃₇ N ₃ O ₂	413	2.6*	6
341	2043	C ₂₄ H ₃₁ N ₃ O ₂	394	6.8* ,	17

Table 5 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
342	2044	C ₂₅ H ₂₈ N ₄ O ₄	449	8.7*	16
343	2045	C ₂₆ H ₂₉ CIN ₆ O ₄	525	11.4*	19
344	2046	C ₂₇ H ₃₂ N ₆ O ₄	505	7.7*	13
345	2047	C ₂₈ H ₃₂ N ₄ O ₄	489	10.0*	18
346	2048	C ₂₈ H ₃₇ N ₅ O ₅	524	3.7*	6
347	2049	C ₂₈ H ₃₇ N ₅ O ₄	509	5.3*	9
Note	: * indicated "yiel	d (mg) of trifluoroaceta	ate".		

[Example 348] Synthesis of (R)-1-(4-chlorobenzyl)-3-[[N-(2-amino-5-chlorobenzoyl)glycyl]amino]pyrrolidine (Compd. No. 1084)

[0137] 2-Amino-5-chlorobenzoic acid (0.060 mL) and diisopropylcarbodiimide (0.060 mol) were added to a chloroform (2 mL) solution of (R)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (0.050 mmol). The resulting reaction solution was stirred at room temperature for 15 hours. The mixture solution was loaded onto a Varian™ SCX column and washed with methanol (15 mL). The obtained crude product was eluted with a solution of 2 M NH₃ in methanol (5 mL) and concentrated to thereby afford (R)-1-(4-chlorobenzyl)-3-[N-[2-amino-5-chlorobenzoyl]glycyl]amino]pyrrolidine (Compd. No. 1084) (12.7 mg, 60%). The purity was determined by RPLC/MS (87%). ESI/MS m/e 421.0 (M++H, C₂₀H₂₂Cl₂N₄O₂).

[Examples 349 to 361]

Q means "Quantitative".

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[0138] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 348. When the starting amine remained, a chloroform (1 mL) solution of an isocyanatomethylated polystyrene (50 mg) was added and reacted at room temperature. The resulting reaction mixtures were filtered and concentrated to thereby afford the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 6.

Table 6

	Table 6					
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)	
349	1085	C ₂₀ H ₂₂ CIN ₅ O ₄	432.0	4.1	19	
350	1086	C ₂₀ H ₂₃ CIN ₄ O ₂	387.0	7.9	41	
351	1087	C ₂₂ H ₂₃ CIN ₄ O ₂	411.0	15.0	73	
352	1088	C ₁₈ H ₂₀ ClN ₃ O ₃	362.0	12.9	71	
353	1089	C ₂₂ H ₂₂ CIFN ₄ O ₂	429.0	16.0	75	
354	1090	C ₂₂ H ₂₆ CIN ₃ O ₃	416.0	15.8	76	
355	1091	C ₂₁ H ₂₄ Cl ₂ N ₄ O ₂	435.0	10.9	50	
356	1092	C ₂₁ H ₂₄ CIN ₅ O ₄	446.0	7.9	35	
357	1093	C ₂₁ H ₂₅ Cl ₄ O ₂	. 401.0	9.5	47	
358	1094	C ₂₃ H ₂₅ CIN ₄ O ₂	425.0	15.8	74	
359	1095	C ₁₉ H ₂₂ CIN ₃ O ₃	376.0	13.5	72	
360	1096	C ₂₃ H ₂₄ CIFN ₄ O ₂	443.0	11.8	53	
361	1097	C ₂₃ H ₂₈ CIN ₃ O ₃	430.0	15.1	70	

[Example 362] Synthesis of (R)-1-(4-chlorobenzyl-3-[[N-(3-bromo-4-methylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 1098)

[0139] 3-Brmo-4-methylbenzoic acid (0.060 mL), diisopropylcarbodiimide (0.060 mmol) and HOBt (0.060 mmol) were added to a solution of (R)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (0.050 mmol) in chloroform (1.35 mL) and tertbutanol (0.15 mL). The resulting reaction mixture was stirred at room temperature for 15 hours. The mixture solution was loaded onto a Varian™ SCX column and washed with methanol/chloroform =1:1 (12 mL) and methanol (12 mL). The crude product was eluted with a solution of 2 M NH₃ in methanol (5 mL) and concentrated to thereby provide (R)-1-(4-chlorobenzyl)-3-[[N-(3-bromo-4-methylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 1098) (11.6 mg, 50%). The purity was determined by RPLC/MS (94%). ESI/MS m/e 466.0 (M++H, C₂₁H₂₃BrCIN₃O₂).

[Examples 363 to 572]

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[0140] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 362. The obtained products, if necessary, were purified by preparative TLC to afford the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 7.

[0141] The following three compounds were obtained as by-products of the Compd. Nos. 1415, 1416 and 1417.

[0142] Compd. No. 1419: 7.9 mg, yield 38%, ESI/MS m/e 419.0 (C₂₀H₂₃CIN₄O₂S).

Compd. No. 1420: 7.1mg, yield 36%, ESI/MS m/e 399.2 ($C_{23}H_{26}N_4O_2S$). [0143]

[0144] Compd. No. 1421: 7.4 mg, yield 37%, ESI/MS m/e 404.2 (C₁₉H₂₅N₅O₃S).

		Table 7			
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
363	1099	C ₂₀ H ₂₀ BrCIFN ₃ O ₂	470.0	3.1	13
364	1100	C ₂₀ H ₂₀ Cl ₂ FN ₃ O ₂	424.0	3.1	15
365	1101	C ₂₁ H ₂₃ CIIN ₃ O ₂	512.0	12.5	49
366 .	1102	C ₂₁ H ₂₃ CIN ₄ O ₄	431.2	7.7	36
367	1103	C ₂₂ H ₂₆ BrN ₃ O ₂	446.0	13.8	62
368	1104	C ₂₁ H ₂₃ BrFN ₃ O ₂	450.0	16.5	74
369	1105	C ₂₁ H ₂₃ CIFN ₃ O ₂	404.2	14.7	73
370	1106	C ₂₂ H ₂₆ IN ₃ O ₂	492.0	18.5	75
371	1107	C ₂₂ H ₂₆ N ₄ O ₄	411.2	15.2	74
372	1108	C ₂₀ H ₂₅ BrN ₄ O ₃	449.0	12.8	57
373	1109	C ₁₉ H ₂₂ BrFN ₄ O ₃	455.0	16.2	71
374	1110	C ₁₉ H ₂₂ CIFN ₄ O ₃	409.2	14.4	70
375	1111	C ₂₀ H ₂₅ IN ₄ O ₃	497.0	17.9	72
376	1112	C ₂₀ H ₂₅ N ₅ O ₅	416.2	14.9	72
377	1113	C ₂₃ H ₂₇ BrClN ₃ O ₂	494.0	16.1	65
378	1114	C ₂₂ H ₂₄ BrCIFN ₃ O ₂	498.0	20.2	81
379	1115	C ₂₂ H ₂₄ Cl ₂ FN ₃ O ₂	452.2	18.6	82
380	1116	C ₂₃ H ₂₇ CIIN ₃ O ₂	539.1	21.9	81
381	1117	C ₂₃ H ₂₇ CIN ₄ O ₄	459.2	18.7	81
382	1171	C ₂₁ H ₂₃ BrClN ₃ O ₂	466.0	4.9	21
383	1172	C ₂₂ H ₂₃ CIN ₄ O ₃	427.2	16.1	75
384	1173	C ₂₃ H ₂₅ CIN ₄ O ₃	441.2	22.8	Q
385	1174	C ₂₀ H ₂₂ CIFN ₄ O ₂	405.2	21.4	Q

Table 7 (continued)

	,	Table / (Conti		,	
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
386	1175	C ₂₂ H ₂₆ BrN ₃ O ₂	446.0	15.8	71
387	1176	C ₂₃ H ₂₆ N ₄ O ₃	407.2	17.6	87
388	1177	C ₂₄ H ₂₈ N ₄ O ₃	421.2	20.2	96
389	1178	C ₂₁ H ₂₅ FN ₄ O ₂	385.0	16.2	84
390	1179	C ₂₁ H ₂₅ N ₅ O ₄	412.2	2.3 [.]	11
391	1180	C ₂₃ H ₂₆ N ₄ O ₂	391.0	21.6	Q
392	1181	C ₂₀ H ₂₅ BrN₄O ₃	451.0	20.1	89
393	1182	C ₂₁ H ₂₅ N ₅ O ₄	412.2	13.3	65
394	1183	C ₂₂ H ₂₇ N ₅ O ₄	426.2	20.9	98
395	1184	C ₁₉ H ₂₄ FN ₅ O ₃	390.0	20.0	Q
396	1185	C ₁₉ H ₂₄ N ₆ O ₅	417.2	18.2	87
397	1186	C ₂₁ H ₂₅ N ₅ O ₃	396.2	17.6	89
398	1187	C ₂₃ H ₂₇ BrClN ₃ O ₂	494.0	22.1	90
399	1188	C ₂₄ H ₂₇ CIN ₄ O ₃	455.2	17.2	76
400	1189	C ₂₅ H ₂₉ CIN ₄ O ₃	469.2	21.1	90
401	1190	C ₂₂ H ₂₆ CIFN ₄ O ₂	433.2	20.4	94
402	1217	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	38.5	81
403	1218	C ₂₁ H ₂₃ CIFN ₃ O ₂	404.2	35.6	88
404	1219	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	3.7	9
405	1220	C ₂₀ H ₂₂ CIIN ₄ O ₂	513.0	53.0	Q
406	1221	C ₂₀ H ₂₁ CIF ₂ N ₄ O ₂	423.0	38.7	92
407	1222	C ₁₉ H ₂₃ CIN ₄ O ₂	375.2	33.6	90
408	1223	C ₂₆ H ₂₆ CIN ₃ O ₂ S	496.0	43.7	88
409	1224	C ₂₀ H ₂₁ CIN ₄ O ₅	433.0	40.6	94
410	1225	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	454.2	18.4	41
411	1226	C ₂₂ H ₂₆ FN ₃ O ₂	384.0	17.1	45
412	1227	C ₂₂ H ₂₆ CIN ₃ O ₂	400.2	17.5	44
413	1228	C ₂₁ H ₂₅ IN ₄ O ₂	493.0	23.3	47
414	1229	C ₂₁ H ₂₄ F ₂ N ₄ O ₂	403.2	18.4	46
415	1230	C ₂₀ H ₂₆ N ₄ O ₂	355.2	15.7	44
416	1231	C ₂₇ H ₂₉ N ₃ O ₂ S	476.0	20.9	88
417	1232	C ₂₁ H ₂₄ N ₄ O ₅	413.0	19.9	96
418	1233	C ₂₀ H ₂₂ CIF ₃ N ₄ O ₃	459.0	19.4	85
419	1234	C ₂₀ H ₂₅ FN ₄ O ₃	389.0	17.8	92
420	1235	C ₂₀ H ₂₅ CIN ₄ O ₃	405.2	18.7	92
421	1236	C ₁₉ H ₂₄ IN ₅ O ₃	498.0	23.9	96
422	1237	C ₁₉ H ₂₃ F ₂ N ₅ O ₃	408.2	19.0	93
423	1238	C ₁₈ H ₂₅ N ₅ O ₃	360.0	16.3	91

Table 7 (continued)

		Table 7 (conti	naca,		
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
424	1239	C ₂₅ H ₂₈ N ₄ O ₃ S	481.2	21.4	89
425	1240	C ₁₉ H ₂₃ N ₅ O ₆	418.0	19.9	95
426	1241	C ₂₃ H ₂₄ Cl ₂ F ₃ N ₃ O ₂	502.0	22.5	90
427	1242	C ₂₃ H ₂₇ CIFN ₃ O ₂	432.2	21.2	98
428	1243	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂	448.0	21.6	96
429	1244	C ₂₂ H ₂₆ CllN ₄ O ₂	541.0	26.4	98
430	1245	C ₂₂ H ₂₅ CIF ₂ N ₄ O ₂	451.0	21.3	94
431	1246	C ₂₁ H ₂₇ CIN ₄ O ₂	403.2	19.4	96
432	1247	C ₂₈ H ₃₀ ClN ₃ O ₂ S	524.0	24.7	94
433	1248	C ₂₂ H ₂₅ CIN ₄ O ₅	461.0	20.7	90
434	1249	C ₂₀ H ₂₀ Cl ₂ N ₄ O ₄	451.0	7.4	33
435	1250	C ₂₁ H ₂₃ CIN ₄ O ₄	431.2	15.5	72
436	1251	C ₁₉ H ₂₂ CIN ₅ O ₅	436.0	22.9	Q
437	1252	C ₂₃ H ₂₈ CIN ₃ O ₂	414.2	17.9	86
438	1253	C ₂₄ H ₃₁ N ₃ O ₂	394.2	15.8	80
439	1254	C ₂₂ H ₃₀ N ₄ O ₃	399.2	17.3	87
440	1255	C ₂₀ H ₂₂ BrClN ₄ O ₂	467.0	21.3	91
441	1256	C ₂₁ H ₂₅ BrN ₄ O ₂	445.0	20.7	93
442	1257	C ₁₉ H ₂₄ BrN ₅ O ₃	450.0	21.8	97
443	1258	C ₂₁ H ₂₅ CIN ₄ O ₂	401.2	18.1	90
444	1259	C ₁₉ H ₂₄ CIN ₅ O ₃	406.0	20.1	99
445	1260	C ₂₃ H ₂₉ N ₃ O ₃	396.2	16.8	85
446	1261	C ₂₃ H ₃₀ CIN ₃ O ₃	432.2	19.8	92
447	1262	C ₂₄ H ₃₃ N ₃ O ₃	412.2	17.4	85
448	1263	C ₂₂ H ₃₂ N ₄ O ₄	417.2	18.7	90
449	1264	C ₂₅ H ₂₆ CIN ₃ O ₃	452.2	29.1	Q
450	1265	C ₂₆ H ₂₉ N ₃ O ₃	432.2	18.1	8 ⁻ 4
451	1266	C ₂₄ H ₂₈ N ₄ O ₄	437.2	19.3	88
452	1267	C ₂₃ H ₂₂ CIF ₃ N ₄ O ₃	495.2	20.6	83
453	1268	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₃	436.0	17.5	80
454	1269	C ₂₀ H ₂₁ BrClN ₃ O ₃	468.0	19.2	82
455	1270	C ₂₀ H ₂₁ Cl ₂ N ₃ O ₃	422.2	17.3	82
456	1271	C ₂₀ H ₂₀ CIFN ₄ O ₄	435.0	17.1	79
457	1272	C ₂₄ H ₂₅ F ₃ N ₄ O ₃	475.2	21.7	91
458	1273	C ₂₂ H ₂₆ CIN ₃ O ₃	416.2	17.8	86
459	1274	C ₂₁ H ₂₄ BrN ₃ O ₃	448.0	19.5	. 87
460	1275	C ₂₁ H ₂₄ CIN ₃ O ₃	402.2	16.7	83
461	1276	C ₂₁ H ₂₃ FN ₄ O ₄	415.2	18.1	87

Table 7 (continued)

		Table / (conti	,		
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
462	1277	C ₂₂ H ₂₄ F ₃ N ₅ O ₄	480.2	20.3	85
463	1278	C ₂₀ H ₂₅ CIN ₄ O ₄	421.2	18.6	88
464	1279	C ₁₉ H ₂₃ BrN ₄ O ₄	451.0	21.3	94
465	1280	C ₁₉ H ₂₃ CIN ₄ O ₄	407.2	19.1	94
466	1281	C ₁₉ H ₂₂ FN ₅ O ₅	420.2	19.1	91
467	1282	C ₂₅ H ₂₆ ClF ₃ N ₄ O ₃	523.2	25.0	96
468	1283	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₃	464.2	12.2	53
469	1284	C ₂₂ H ₂₅ BrClN ₃ O ₃	496.0	24.1	97
470	1285	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₃	450.2	21.8	97
471	1321	C ₂₀ H ₂₀ BrCl ₂ N ₃ O ₂	486.0	5.1	21
472	1322	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	10.5	50
473	1323	C ₂₀ H ₂₀ Cl ₂ IN ₃ O ₂	532.0	7.1	27
474	1324	C ₂₁ H ₂₄ CIN ₃ O ₃	402.2	22.2	Q
475	1325	C ₂₇ H ₂₆ CIN ₃ O ₃	476.0	22.2	93
476	1326	C ₂₀ H ₂₁ CIIN ₃ O ₃	514.0	26.9	Q
477	1327	C ₂₁ H ₂₅ CIN ₄ O ₂	401.2	24.2	Q
478	1328	C ₂₁ H ₂₃ BrClN ₃ O ₂	466.0	23.1	99
479	1329	C ₂₂ H ₂₆ CIN ₃ O ₂	400.2	16.4	82
480	1330	C ₂₁ H ₂₃ CIIN ₃ O ₂	512.2	20.8	81
481	1331	C ₂₁ H ₂₄ N ₃ O ₃	382.2	19.6	Q
482	1332	C ₂₈ H ₂₉ N ₃ O ₃	456.2	21.1	93
483	1333	C ₂₁ H ₂₄ IN ₃ O ₃	494.0	25.3	Q
484	1334	C ₂₂ H ₂₈ N ₄ O ₂	381.2	19.0	Q
485	1335	C ₁₉ H ₂₂ BrClN ₄ O ₃	471.0	25.8	Q
486	1336	C ₂₀ H ₂₅ CIN ₄ O ₃	405.2	18.5	91
487	1337	C ₁₉ H ₂₂ CIIN ₄ O ₃	517.0	23.1	89
488	1338	C ₂₀ H ₂₆ N ₄ O ₄	387.2	20.6	Q
489	1339	C ₂₆ H ₂₈ N ₄ O ₄	461.2	23.7	Q.
490	1340	C ₁₉ H ₂₃ IN ₄ O ₄	499.0	28.2	Q
491	1341	C ₂₀ H ₂₆ N ₄ O ₄	386.0	20.5	Q
492	1342	C ₂₂ H ₂₄ BrCl ₂ N ₃ O ₂	514.0	27.2	Q
493	1343	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂	448.0	21.4	95
494	1344	C ₂₂ H ₂₄ Cl ₂ IN ₃ O ₂	560.0	27.0	96
495	1345	C ₂₃ H ₂₈ CIN ₃ O ₃	430.2	23.8	Q
496	1346	C ₂₂ H ₂₅ CIIN ₃ O ₃	542.0	29.4	Q
497	1347	C ₁₉ H ₂₂ ClN ₃ O ₂ S	392.0	16.9	43
498	1348	C ₂₀ H ₂₅ N ₃ O ₂ S	372.2	6.9	19
499	1349	C ₁₈ H ₂₄ N ₄ O ₃ S	377.2	8.1	43

Table 7 (continued)

		Table 7 (COIIII			
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
500	1350	C ₂₁ H ₂₆ CIN ₃ O ₂ S	420.0	13.0	62
501	1351	C ₂₂ H ₂₄ BrCIN ₄ O ₃	509.2	5.0	10
502	1352	C ₂₃ H ₂₇ BrN ₄ O ₃	489.2	3.6	15
503	1353	C ₂₁ H ₂₆ BrN ₅ O ₄	494.0	2.8	11
504	1354	C ₂₄ H ₂₈ BrClN ₄ O ₃	537.2	5.2	19
505	1355	C ₂₁ H ₂₂ CIN ₅ O ₂	412.0	25.5	Q
506	1356	C ₂₂ H ₂₅ N ₅ O ₂	392.0	16.5	84
507	1357	C ₂₀ H ₂₄ N ₆ O ₃	397.2	19.9	Q
508	1358	C ₂₃ H ₂₆ CIN ₅ O ₂	440.2	21.8	99.
509	1368	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	18.4	78
510	1369	C ₂₄ H ₂₄ CIF ₆ IN ₃ O ₄	568.0	24.1	85
511	1370	C ₁₈ H ₁₉ BrClN ₃ O ₂ S	458.0	19.4	85
512	1371	C ₂₆ H ₂₆ CIN ₃ O ₄ S	512.2	22.1	86
513	1372	C ₂₆ H ₂₆ CIN ₃ O ₂	448.0	19.1	85
514	1373	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	454.2	16.2	71
515	1374	C ₂₅ H ₂₇ F ₆ IN ₃ O ₄	548.2	22.1	81
516	1375	C ₁₉ H ₂₂ BrN ₃ O ₂ S	436.0	17.1	78
517	1376	C ₂₇ H ₂₉ N ₃ O ₄ S	492.0	19.4	79
518	1377	C ₂₇ H ₂₉ N ₃ O ₂	428.2	18.1	85
519	1378	C ₂₀ H ₂₂ CIF ₃ N ₄ O ₃	459.0	17.3	75
520	1379	C ₂₃ H ₂₆ F ₆ IN ₄ O ₅	553.2	21.0	76
521	1380	C ₁₇ H ₂₁ BrN ₄ O ₃ S	443.0	16.4	74
522	1381	C ₂₅ H ₂₈ N ₄ O ₅ S	497.0	18.4	74
523	1382	C ₂₅ H ₂₈ N ₄ O ₃	433.2	17.3	80
524	1383	C ₂₃ H ₂₄ Cl ₂ F ₃ N ₃ O ₂	502.0	20.0	80
525	1384	C ₂₀ H ₂₃ BrClN ₃ O ₂ S	486.0	21.0	87
526	1385	C ₂₈ H ₃₀ CIN ₃ O ₄ S	540.2	23.8	88
527	1386	C ₂₈ H ₃₀ CIN ₃ O ₂	476.0	20.0	84
528	1411	C ₂₂ H ₂₄ Cl ₂ N ₄ O ₃	463.0	0.4	2
529	1412	C ₂₃ H ₂₇ CIN ₄ O ₂	443.0	1.3	6
530	1413	C ₂₁ H ₂₆ CIN ₅ O ₄	448.0	1.1	5
531	1414	C ₂₄ H ₂₈ Cl ₂ N ₄ O ₃	491.0	0.8	3
532	1415	C ₂₁ H ₂₂ CIN ₅ O ₂ S	444.0	6.8	31
533	1416	C ₂₂ H ₂₅ N ₅ O ₂ S	424.0	4.8	23
534	1417	C ₂₀ H ₂₄ N ₆ O ₃ S	429.2	4.5	21 .
535	1418	C ₂₃ H ₂₆ CIN ₅ O ₂ S	472.0	10.4	44
536	1423	C ₂₇ H ₂₆ CIN ₃ O ₃	476.0	23.9	Q
537	1424	C ₂₇ H ₂₉ N ₃ O ₄ S	456.2	28.0	Q

Table 7 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
538	1425	C ₂₆ H ₂₈ N ₄ O ₄	461.2	22.3	97
539	1426	C ₂₉ H ₃₀ CIN ₃ O ₃	504.2	26.8	Q
540	1583	C ₂₁ H ₂₂ CIF ₃ N ₄ O ₂	455.0	14.6	64
541	1584	C ₂₁ H ₂₂ CIF ₃ N ₄ O ₃	471.0	17.4	74
542	1585	C ₁₉ H ₂₀ BrClN ₄ O ₂	453.0	15.6	69
543	1586	C ₁₉ H ₂₀ Cl ₂ N ₄ O ₂	407.2	2.3	` 11
544	1587	C ₂₆ H ₂₆ CIN ₃ O ₃	464.0	15.4	66
545	1588	C ₂₀ H ₂₃ CIN ₄ O ₂	387.0	14.8	77
546	1589	C ₂₂ H ₂₅ F ₃ N ₄ O ₂	435.2	11.1	51
547	1590	C ₂₀ H ₂₅ F ₃ N ₄ O ₃	451.2	16.3	72
548	1591	C ₂₀ H ₂₃ BrN ₄ O ₂	433.0	15.4	71
549	1592	C ₂₀ H ₂₃ CIN ₄ O ₂	387.0	15.6	81
550	1593	C ₂₇ H ₂₉ N ₃ O ₃	444.2	14.8	67
551	1594	C ₂₀ H ₂₄ F ₃ N ₅ O ₃	440.2	16.2	74
552	1595	C ₂₀ H ₂₄ F ₃ N ₅ O ₄	456.2	15.4	68
553	1596	C ₁₈ H ₂₂ BrN ₅ O ₃	436.0	15.6	72
554	1597	C ₁₈ H ₂₂ CIN ₅ O ₃	391.8	14.4	73
555	1598	C ₂₅ H ₂₈ N ₄ O ₄	449.2	15.9	71
556	1599	C ₁₉ H ₂₅ N ₅ O ₃	372.2	15.8	85
557	1606	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₂ S	472.0	17.0	72
558	1607	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₂ S	452.2	15.3	68
559	1608	C ₂₀ H ₂₃ F ₃ N ₄ O ₃ S	457.2	15.9	70
560	1660	C ₂₁ H ₂₂ BrF ₃ N ₄ O ₂	501.0	19.0	76
561	1661	C ₂₁ H ₂₂ BrF ₃ N ₄ O ₃	517.0	16.2	63
562	1662	C ₂₀ H ₂₁ BrF ₂ N ₄ O ₂	469.0	15.1	65
563	1663	C ₂₀ H ₂₂ BrClN ₄ O ₂	467.0	14.5	62
564	1692	C ₂₀ H ₂₃ Br ₂ N ₃ O ₃	514	7.3	28
565	1693	C ₂₂ H ₂₆ F ₂ N ₄ O ₂	417	16.2	78
566	1694	C ₂₂ H ₂₇ FN ₄ O ₂	399	21.8	Q
567	1695	C ₂₂ H ₂₇ BrN ₄ O ₂	459	24.5	Q
568	1696	C ₂₂ H ₂₇ IN ₄ O ₂	507	27.4	Q
569	1697	C ₂₂ H ₂₇ CIN ₄ O ₂	415	22.1	Q
570	1698	C ₂₃ H ₂₇ F ₃ N ₄ O ₃	465	24.3	Q
571	1699	C ₂₃ H ₂₇ F ₃ N ₄ O ₂	449	25.3	Q
572	1700	C ₂₂ H ₂₅ BrClN ₃ O ₂	480	17.8	74
Note:	Q means "Quar	ntitative".			

[0145] For example, Compd. No. 1583 exhibited the following NMR: 1H NMR (400MHz, CD₃OD) δ 1.64-1.72 (m, 1 H), 2.20-2.30 (m, 1 H), 2.41-2.51 (m, 2 H), 2.71-2.78 (m, 2 H), 3.59 (dd, J = 15.4, 12.9 Hz, 2 H), 3.94 (s, 2 H), 4.35-4.41

(m, 1 H), 6.82 (d, J = 8.6 Hz, 1 H), 7.29 (s, 4 H), 7.40 (dd, J = 8.6, 1.7 Hz, 1 H), 7.85 (d, J = 0.96 Hz, 1 H).

[Reference Example 4] Synthesis of (S)-3-[N-[3-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine

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- [0146] A suspension of (S)-1-(4-chlorobenzyl)-3-[N-[3-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine (2.93 g. 6.66 mmol) and Pd(OH) 2 in a 5% formic acid/methanol (70 mL) was stirred at 60 °C for 3 hours. The palladium catalyst was removed by filtration through Celite to concentrate the filtrate. A 2 M solution of NaOH (100 mL) was added to the resulting residue, and the resulting mixture was extracted with ethyl acetate (100mL×3). The extracts were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography
 [SiO₂, ethyl acetate/methanol/triethylamine = (85:10:5) to (60:30:5)] to thereby provide (S)-3-[N-3-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine (1.70 g, 81%) as an oil. ¹H NMR (CDCl₃, 270MHz) δ 1.76 (d, J = 7.3 Hz, 1 H), 2.07-2.25 (m, 1H), 2.81-2.98 (m, 2 H), 3.02-3.11 (m, 2 H), 4.12 (s, 2 H), 4.41 (br, 1 H), 6.90 (br, 1 H), 7.45 (br, 1 H), 7.58 (dd, J = 7.3 and 7.3 Hz, 1 H), 7.77 (d, J = 7.3 Hz, 1 H), 8.02 (d, J = 7.3 Hz, 1 H), 8.11 (s, 1 H); ESI/MS m/e 316.0 (M*+H, C₁₄H₁₆F₃N₃O₂).
- [0147] Further, (R)-3-[N-[3-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine was synthesized by using the corresponding starting material and reactants according to the above method. 1.49 g, 68%. The product exhibited the same ¹H NMR and ESI/MS as those of the (S)-isomer.
 - **[0148]** In addition, (R)-3-[N-[2-amino-5-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine was synthesized by using the corresponding starting material and reactants according to the above method. 316 mg, 93%; ESI/MS m/e 331.2 (M++H, $C_{14}H_{17}F_3N_4O_2$).
 - [0149] Moreover, (R)-3-[N-[2-(tert-butoxycarbonylamino)-5-(trifluoromethoxyl)benzoyl]glycyl]aminopyrrolidine was synthesized by using the corresponding starting material and reactants according to the above method. Quantitative yield; 1 H NMR (CDCl₃, 400MHz) δ 1.51 (s, 9 H), 1.60-1.70 (m, 2 H), 2.10-2.25 (m, 1 H), 2.80-2.88 (m, 1 H), 2.89-2.98 (m, 1 H), 3.04-3.18 (m, 2 H), 4.05 (d, J = 4.9 Hz, 2 H), 4.43 (br, 1 H), 6.15 (br, 1 H), 7.03 (br, 1 H), 7.32 (d, J = 9.3 Hz, 1 H), 7.38 (s, 1 H), 8.42 (d, J = 9.3 Hz, 1 H).

[Example 573] Synthesis of (R)-3-[[N-[2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl]glycyl]amino]-1-(4-chlorobenzyl)pyrrolidine

[0150] Triethylamine (2.9 mL, 20.5 mmol), 2-(tert-butoxycarbonylamino)-5-(trifluoromethyl)benzoic acid (6.27 g, 20.5 mmol), EDCI (3.9 g, 20.5 mmol) and HOBt (2.8 g, 20.5 mmol) were added to a dichloromethane (100 mL) solution of (R)-1-(4-chlorobenzyl)-3-(glycylamino)pyrrolidine (5.0 g, 18.7 mmol). The resulting reaction mixture was stirred at room temperature overnight. A 2 M aqueous solution (80 mL) of NaOH was added to the reaction mixture, and the resulting mixture was extracted with dichloromethane. The obtained extract was dried over anhydrous Na₂SO₄, filtered, concentrated and purified by column chromatography [SiO₂, hexane/ethyl acetate = (1:1) to (1:4)] to thereby afford (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4-chlorobenzyl)pyrrolidine (9.41 g, 91%) as a white amorphous solid. ESI/MS m/e 555.2 (M++H, C₂₆H₃₀CIF₃N₄O₄).

[Reference Example 5] Synthesis of (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino] pyrrolidine

[0151] A mixture of (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4-chlorobenzyl)pyrrolidine (6.3 g, 11.4 mmol) with Pd(OH) $_2$ (1.68 g), formic acid (3.7 mL) and methanol (80 mL) was stirred at 50 °C overnight. The mixture was cooled to room temperature, and the palladium catalyst was then removed by filtration through Celite. The resulting filtrate was concentrated and purified by column chromatography [SiO $_2$, ethyl acetate/methanol = (5:1) to (4:1)] to thereby provide (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl] amino]pyrrolidine (4.42 g, 90%) as a white solid. 1 H NMR (CDCl $_3$, 400MHz) δ 1.48 (s, 9 H), 2.0-2.4 (m, 2 H), 3.42-3.71 (m, 5 H), 4.00-4.22 (m, 2 H), 4.56 (br, 1 H), 7.48 (d, J = 9.0 Hz, 1 H), 7.93 (s, 1 H), 8.17 (br, 1 H), 8.33 (d, J = 9.0 Hz, 1 H), 8.45 (br, 1 H).

[Example 574] Synthesis of (S)-1-benzyl-3-[N-[3-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine (Compd. No. 239)

[0152] An acetonitrile (1.1 mL) solution of (S)-3-[N-[3-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine (0.06 mmol) and a (piperidinomethyl)polystyrene (2.6 to 2.8 mmol/g, 30 mg) were added to an acetonitrile (0.4 mL) solution of benzyl bromide (0.050 mmol). The resulting reaction mixture was stirred at 45 °C for 5 hours. The mixture solution was cooled to room temperature, and the resin was then removed by filtration to concentrate the filtrate. The resulting residue was dissolved in acetonitrile (1.0 mL), and phenyl isocyanate (0.008 mL, 0.05 mmol) was then added to the obtained solution. The mixture solution was stirred at room temperature for 1 hour, loaded onto a VarianTM SCX column

and washed with methanol (15 mL). The obtained crude product was eluted with a solution of 2 M NH $_3$ in methanol (6 mL) and concentrated to thereby provide (S)-1-benzyl-3-[N-[3-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine (Compd. No. 239) (9.0 mg, 44%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 406.0 (M++H, $C_{21}H_{22}F_3N_3O_2$).

[Example 575] Synthesis of (R)-1-(4-butylbenzyl)-3-[[N-(3-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 1648)

[0153] Acetic acid (0.060 mL) was added to a mixture of (R)-3-[N-[3-(trifluoromethyl)benzoyl]glycyl]aminopyrrolidine (0.050 mL) with 4-butylbenzaldehyde (0.18 mmol), NaBH₃CN (0.23 mmol) and methanol (1.85 mL). The resulting reaction mixture was stirred at 60 °C for 12 hours, cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol (15 mL). The obtained crude product was eluted with a solution of 2 M NH₃ in methanol (5 mL) and concentrated to thereby afford (R)-1-(4-butylbenzyl)-3-[[N-(3-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 1648) (20.6 mg, 89%). The purity was determined by RPLC/MS (91%). ESI/MS m/e 462.2 (M*+H, C₂₅H₃₀F₃N₃O₂).

[Examples 576 to 738]

[0154] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 574 or 575. The obtained crude products, if necessary, were purified by preparative TLC or chromatography (HPLC-C₁₈) to provide the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 8.

Table 8

Table 8					
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
576	240	C ₂₁ H ₂₁ F ₄ N ₃ O ₂	424.0	10.2	48
577	241	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₂	440.0	12.1	55
578	242	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	13.9	59
579	243	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	13.8	58
580	244	C ₂₂ H ₂₄ F ₃ N ₃ O ₂	420.0	13.1	62
581	245	C ₂₁ H ₂₁ F ₄ N ₃ O ₂	424.0	11.9	56
582	246	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₂	440.0	8.5	39
583	247	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	10.5	44
584	248	$C_{22}H_{24}CF_3N_3O_3$	436.0	11.0	51
585	249	C ₂₂ H ₂₁ CIF ₆ N ₃ O ₂	474.0	12.8	54
586	250	$C_{22}H_{24}F_3N_3O_2$	420.0	11.0	52
587	251	C ₂₁ H ₂₁ F ₄ N ₃ O ₂	424.0	13.5	64
588	252	C ₂₂ H ₂₄ F ₃ N ₃ O ₃	436.0	11.8	54
589	253	$C_{22}H_{24}F_3N_3O_2$	420.0	11.1	53
590	254	C ₂₁ H ₂₀ CIF ₃ N ₄ O ₄	485.0	. 2.4	10
591	255	C ₂₁ H ₂₁ F ₃ N ₄ O ₄	451.0	12.2	54
592	256	C ₂₁ H ₂₁ F ₃ N ₄ O ₄	451.0	11.4	51
593	257	C ₂₂ H ₂₁ F ₆ N ₃ O ₂	474.0	11.1	47
594	258	C ₂₄ H ₂₆ F ₃ N ₃ O ₄	478.0	15.3	64
595	259	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	420.0	6.4	31
596	260	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	12.1	51
597	261	C ₂₂ H ₂₁ CIF ₆ N ₃ O ₂	474.0	13.6	57

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Table 8 (continued)

		Table 0 (conti	,		
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
598	262	C ₂₁ H ₂₁ BrF ₃ N ₃ O ₂	484.0	15.2	63
599	263	C ₂₁ H ₂₁ BrF ₃ N ₃ O ₂	484.0	14.5	60
600	264	C ₂₇ H ₂₆ F ₃ N ₃ O ₃	498.0	9.3	37
601	265	C ₂₁ H ₂₁ BrF ₃ N ₃ O ₂	484.0	11.6	48
602	266	C ₂₂ H ₂₂ F ₃ N ₃ O ₄	450.0	8.9	40
603	267	C ₂₂ H ₂₄ F ₃ N ₃ O ₃	436.0	10.3	47
604	268	C ₂₃ H ₂₅ F ₃ N ₄ O ₃	463.0	6.3	27
605	269	C ₂₂ H ₂₄ F ₃ N ₃ O ₄ S	484.0	8.0	33
606	270	C ₂₃ H ₂₄ F ₃ N ₃ O ₄	464.0	8.9	38
607	271	C ₂₁ H ₂₀ F ₅ N ₃ O ₂	442.0	6.1	28
608	272	C ₂₁ H ₂₂ F ₃ N ₃ O ₃	422.0	13.6	59
609	273	C ₂₂ H ₂₁ F ₃ N ₄ O ₂	431.0	12.6	59
610	274	C ₂₂ H ₂₁ F ₃ N ₄ O ₂	431.0	7.7	36
611	275	C ₂₂ H ₂₁ F ₃ N ₄ O ₂	431.0	12.7	59
612	276	C ₂₁ H ₂₀ F ₅ N ₃ O ₂	442.0	11.7	53
613	277	C ₂₇ H ₂₆ F ₃ N ₃ O ₂	482.0	9.5	39
614	278	C ₂₃ H ₂₄ F ₃ N ₃ O ₄	464.0	13.0	56
615	279	C ₂₂ H ₂₁ F ₆ N ₃ O ₃	490.0	10.4	42
616	280	C ₂₂ H ₂₁ F ₆ N ₃ O ₃	490.0	12.0	49
617	281	C ₂₂ H ₂₂ F ₃ N ₃ O ₄	450.0	4.9	22
618	282	C ₂₅ H ₃₀ F ₃ N ₃ O ₂	462.0	12.0	52
619	283	C ₂₀ H ₂₃ F ₃ N ₄ O ₃	425.0	8.1	38
620	284	C ₂₇ H ₂₅ CIF ₃ N ₃ O ₂	516.0	4.8	19
621	285	C ₂₁ H ₂₂ F ₃ N ₃ O ₂	406.0	4.8	. 24
622	286	C ₂₁ H ₂₁ F ₄ N ₃ O ₂	424.0	4.5	21
623	287	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₂	440.0	5.8	26
624	288	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	8.1	34
625	289	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	8.0	34
626	290	C ₂₂ H ₂₄ F ₃ N ₃ O ₂	420.0	6.0	29
627	291	C ₂₁ H ₂₁ F ₄ N ₃ O ₂	424.0	6.2	29
628	292	C ₂₁ H ₂₁ CIF ₃ N ₃ O ₂	440.0	4.5	20
629	293	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	5.1	22
630	294	C ₂₂ H ₂₄ CF ₃ N ₃ O ₃	436.0	4.2	19
631	295	C ₂₂ H ₂₁ CIF ₆ N ₃ O ₂	474.0	6.0	25
632	296	C ₂₂ H ₂₄ F ₃ N ₃ O ₂	420.0	4.3	21
633	297	C ₂₁ H ₂₁ F ₄ N ₃ O ₂	424.0	8.2	39
634	298	C ₂₂ H ₂₄ F ₃ N ₃ O ₃	436.0	12.2	56
635	299	$C_{22}H_{24}F_3N_3O_2$	420.0	8.1	39

Table 8 (continued)

		Table 6 (COIIII	nucu)		
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
636	300	C ₂₁ H ₂₀ CIF ₃ N ₄ O ₄	485.0	13.7	57
637	301	C ₂₁ H ₂₁ F ₃ N ₄ O ₄	451.0	15.1	67
638	302	C ₂₁ H ₂₁ F ₃ N ₄ O ₄	451.0	16.6	74
639	303	C ₂₂ H ₂₁ F ₆ N ₃ O ₂	474.0	12.6	53
640	304	C ₂₄ H ₂₆ F ₃ N ₃ O ₄	478.0	14.5	61
641	305	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	420.0	8.4	37
642	306	C ₂₁ H ₂₀ Cl ₂ F ₃ N ₃ O ₂	474.0	13.5	57
643	307	C ₂₂ H ₂₁ CIF ₆ N ₃ O ₂	474.0	3.7	16
644	308	C ₂₁ H ₂₁ BrF ₃ N ₃ O ₂	484.0	7.2	30
645	309	C ₂₁ H ₂₁ BrF ₃ N ₃ O ₂	484.0	6.7	28
646	310	C ₂₇ H ₂₆ F ₃ N ₃ O ₃	498.0	4.2	17
647	311	C ₂₁ H ₂₁ BrF ₃ N ₃ O ₂	484.0	6.3	26
648	312	C ₂₂ H ₂₂ F ₃ N ₃ O ₄	450.0	2.4	11
649	313	C ₂₂ H ₂₄ F ₃ N ₃ O ₃	436.0	1.9	9
650	314	C ₂₃ H ₂₅ F ₃ N ₄ O ₃	463.0	5.0	.22
651	315	C ₂₂ H ₂₄ F ₃ N ₃ O ₄ S	484.0	2.5	10
652	316	C ₂₃ H ₂₄ F ₃ N ₃ O ₄	464.0	3.3	14
653	317	C ₂₁ H ₂₀ F ₅ N ₃ O ₂	442.0	4.5	20
654	318	C ₂₁ H ₂₂ F ₃ N ₃ O ₃	422.0	7.9	34
655	319	C ₂₂ H ₂₁ F ₃ N ₄ O ₂	431.0	6.5	30
656	320	C ₂₂ H ₂₁ F ₃ N ₄ O ₂	431.0	14.2	66
657	321	C ₂₂ H ₂₁ F ₃ N ₄ O ₂	431.0	14.9	69
658	322	C ₂₁ H ₂₀ F ₅ N ₃ O ₂	442.0	13.6	62
659	323	C ₂₇ H ₂₆ F ₃ N ₃ O ₂	482.0	3.9	16
660	324	C ₂₃ H ₂₄ F ₃ N ₃ O ₄	464.0	15.2	66
661	325	C ₂₂ H ₂₁ F ₆ N ₃ O ₃	490.0	16.1	66
662	326	C ₂₂ H ₂₁ F ₆ N ₃ O ₃	490.0	13.6	56
663	327	C ₂₂ H ₂₂ F ₃ N ₃ O ₄	450.0	5.4	24
664	328	C ₂₅ H ₃₀ F ₃ N ₃ O ₂	462.0	10.9	47
665	329	C ₂₀ H ₂₃ F ₃ N ₄ O ₃	425.0	12.0	57
666	986	C ₂₇ H ₂₅ CIF ₃ N ₃ O ₂	516.0	1.5	6
667	1118	C ₂₈ H ₂₇ F ₃ N ₄ O ₃	525	21.5	62
668	1119	C ₂₂ H ₂₄ F ₃ N ₃ O ₂ S	452	16.9	57
669	1120	C ₂₃ H ₂₆ F ₃ N ₃ O ₄	466	20.5	67
670	1121	C ₂₂ H ₂₃ F ₃ N ₄ O ₄	465	16.8	55
671	1122	C ₂₈ H ₃₆ F ₃ N ₃ O ₂	504	21.0	63
672	1123	C ₂₅ H ₂₃ BrF ₃ N ₃ O ₂	534	26.6	75
673	1124	C ₁₉ H ₁₉ F ₃ N ₄ O ₅	441	21.3	73

Table 8 (continued)

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		Table 8 (Conti			
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
674	1133	C ₂₃ H ₂₆ F ₃ N ₃ O ₄	467	33.6	84
675	1134	C ₂₄ H ₂₈ F ₃ N ₃ O ₅	496	34.8	82
676	1135	C ₂₂ H ₂₁ F ₃ N ₄ O ₆	495	32.6	77
677	1136	$C_{23}H_{24}F_3N_3O_5$	480	36.6	89
678	1137	C ₂₂ H ₂₁ BrF ₃ N ₃ O ₄	529	30.8	69
679	1138	C ₂₄ H ₂₆ F ₃ N ₃ O ₂	446	32.7	86
680	1139	C ₂₂ H ₂₄ F ₃ N ₃ O ₂	420	18.6	51
681	1140	C ₂₁ H ₂₀ F ₃ N ₅ O ₆	496	20.5	49
682	1141	C ₂₅ H ₂₄ F ₃ N ₃ O ₂	456	22.5	58
683	1142	C ₂₅ H ₂₄ F ₃ N ₃ O ₂	456	21.6	55
684	1143	C ₃₅ H ₃₄ F ₃ N ₃ O ₄	618	27.3	53
685	1144	C ₂₃ H ₂₆ F ₃ N ₃ O ₄	466	25.5	64
686	1145	C ₂₃ H ₂₅ F ₃ N ₄ O ₆	511	38.0	88
687	1146	C ₂₈ H ₂₈ F ₃ N ₃ O ₃	512	38.3	89
688	1147	C ₂₃ H ₂₅ F ₃ N ₄ O ₃	463	27.1	62
689	1148	C ₂₇ H ₂₆ F ₃ N ₃ O ₂	482	22.4	57
690	1161	C ₂₂ H ₂₄ F ₃ N ₃ O ₄	452	13.5	58
691	1162	C ₂₄ H ₂₈ F ₃ N ₃ O ₃	464	16.7	70
692	1163	C ₂₂ H ₂₃ F ₄ N ₃ O ₃	454	15.8	68
693	1164	C ₂₃ H ₂₆ F ₃ N ₃ O ₃	450	15.7	68
694	1165	C ₂₃ H ₂₄ F ₃ N ₃ O ₄	464	16.3	68
695	1166	C ₂₂ H ₂₃ BrF ₃ N ₃ O ₃	513	15.0	57
696	1168	C ₁₇ H ₁₇ CIF ₃ N ₅ O ₂ S	448	6.9*	23
697	1169	C ₂₀ H ₂₂ F ₃ N ₅ O ₃ S	470	1.7*	6
698	1170	C ₂₂ H ₂₂ F ₃ N ₅ O ₂	446	2.3*	8
699	1286	C ₂₆ H ₃₃ F ₃ N ₄ O ₃	507	25.3*	51
700	1287	C ₂₁ H ₂₀ F ₃ N ₅ O ₆	496	4.0*	8
701	1288	C ₂₂ H ₂₄ F ₃ N ₃ O ₄	452	3.6*	13
702	1298	C ₂₃ H ₂₅ BrF ₃ N ₃ O ₄	544	28.4	Q
703	1299	C ₂₄ H ₂₈ F ₃ N ₃ O ₅	496	1.4	6
704	1300	C ₂₃ H ₂₆ F ₃ N ₃ O ₄	466	7.3	33
705	1301	C ₂₄ H ₂₈ F ₃ N ₃ O ₅	496	12.6	53
706	1302	C ₂₄ H ₂₈ F ₃ N ₃ O ₃	464	24.5	Q
707	1303	C ₂₃ H ₂₅ BrF ₃ N ₃ O ₄	544	22.2	Q
708	1304	C ₂₉ H ₃₀ F ₃ N ₃ O ₄	542	28.6	Q
709	1305	C ₂₆ H ₂₆ F ₃ N ₃ O ₃	486	35.4	Q
710	1306	C ₂₄ H ₂₈ F ₃ N ₃ O ₄	480	8.1	35
711	1307	C ₂₃ H ₂₆ F ₃ N ₃ O ₅	482	27.9	Q

Table 8 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)		
712	1308	C ₂₃ H ₂₄ F ₃ N ₃ O ₃	448	5.9	28		
713	1309	C ₂₃ H ₂₅ F ₃ IN ₃ O ₄	592	24.0	85		
714	1310	C ₂₂ H ₂₄ F ₃ N ₃ O ₄	452	3.4	16		
715	1311	C ₂₂ H ₂₂ F ₃ N ₃ O ₄	450	3.4	16		
716	1312	C ₂₁ H ₂₁ F ₃ IN ₃ O ₂	532	18.1	72		
717	1313	C ₂₁ H ₂₁ BrF ₃ N ₃ O ₂	484	17.4	76		
718	1314	C ₁₉ H ₁₉ F ₃ N ₄ O ₄ S	457	16.8	77		
719	1315	C ₂₀ H ₂₂ F ₃ N ₃ O ₃	410	13.6	70		
720	1316	C ₂₂ H ₂₀ CIF ₆ N ₃ O ₂	508	18.6	77		
721	1317	C ₂₁ H ₂₀ CIF ₃ N ₄ O ₄	485	17.0	74		
722	1318	C ₂₁ H ₂₀ CIF ₄ N ₃ O ₂	458	17.0	78		
723	1319	C ₂₁ H ₂₀ CIF ₄ N ₃ O ₂	458	17.6	81		
724	1320	C ₂₁ H ₂₀ BrF ₄ N ₃ O ₂	502	18.5	77		
725	1390	C ₂₆ H ₃₂ F ₃ N ₃ O ₂	476	16.1	51		
726	1391	C ₂₃ H ₂₆ F ₃ N ₃ O ₂	434	20.0	76		
727	1392	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	454	20.0	67		
728	1393	C ₂₃ H ₂₆ F ₃ N ₃ O ₂	434	20.1	70		
729	1394	C ₂₂ H ₂₃ F ₃ N ₄ O ₄	465	18.4	60		
730	1395	C ₂₃ H ₂₄ F ₃ N ₃ O ₂	432	21.4	75		
731	1396	C ₂₆ H ₂₆ F ₃ N ₃ O ₂	470	20.4	66		
732	1397	C ₂₁ H ₂₀ Br ₂ F ₃ N ₃ O ₂	562	14.5	54		
733	1398	C ₂₂ H ₂₂ Cl ₂ F ₃ N ₃ O ₂	488	10.8	47		
734	1399	C ₂₂ H ₂₂ Cl ₂ F ₃ N ₃ O ₂	488	9.4	40		
735	1400	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	454	19.1	88		
736	1614	C ₂₂ H ₂₁ F ₆ N ₃ S	506.0	24.2	96		
737	2050	$C_{20}H_{22}F_3N_3O_2S$	426	6.0	30		
738	2051	C ₂₁ H ₂₃ F ₃ N ₄ O ₂	421	6.5	32		
	Notes: * indicates "yield (mg) of trifluoroacetate". Q means "Quantitative".						

[Examples 739 to 748]

[0155] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 575. The obtained products, if necessary, were purified with preparative TLC to afford the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 9.

Table 9

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield(mg)	Yield (%)
739	1650	$C_{24}H_{28}F_3N_3O_2$	448.0	20.4	91
740	1706	C ₂₃ H ₂₅ F ₃ N ₄ O ₃	463.2	3.7	11

Table 9 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield(mg)	Yield (%)
741	1707	$C_{22}H_{25}F_3N_4O_2S$	467.0	10.3	29
742	1708	C ₂₃ H ₂₇ F ₃ N ₄ O ₂	449.2	11.4	34
743	1709	C ₂₄ H ₂₉ F ₃ N ₄ O ₂	463.2	15.2	44
744	1775	C ₂₂ H ₂₅ F ₃ N ₄ O ₄	467.2	9.2	26.3
745	1776	C ₂₂ H ₂₅ F ₃ N ₄ O ₄	467.2	8.9	25.4
746	1787	C ₂₄ H ₂₉ F ₃ N ₄ O ₂	463.2	5.6	16.1
747	1802	C ₂₃ H ₂₇ F ₃ N ₄ O ₄	481.2	11.7	32.5
748	1803	C ₂₂ H ₂₅ F ₃ N ₄ O ₃	451.2	9.6	28.4

[Example 749] Synthesis of (R)-3-[[N-2-amino-5-trifluoromethoxybenzoyl)glycyl]amino]-1-(3-hydroxy-4-methoxybenzyl)pyrrolidine (Compd. No. 1896)

[0156] Acetic acid (0.050 mL) was added to a mixture of (R)-3-[N-[2-(tert-butoxycarbonylamino)-5-(trifluoromethoxybenzoyl]glycyl]amino]pyrrolidine (0.050 mmol) with 3-hydroxy-4-methoxybenzaldehyde (0.060 mmol), NaBH₃CN (0.15 mmol) and methanol (1.3 mL). The resulting reaction mixture was stirred at 60 °C for 8 hours, cooled to room temperature, then loaded onto a Varian™ SCX column and washed with methanol (10 mL). The obtained crude product was eluted with a solution of 2 M NH₃ in methanol (5 mL) and concentrated. A 1,4-dioxane solution of 4 M HCl was added to the prepared residue, and the solution was stirred at room temperature overnight, concentrated and then purified by preparative TLC to thereby provide (R)-3-[[N-(2-amino-5-trifluoromethoxybenzoyl)glycyl]amino]-1-(3-hydroxy-4-methoxybenzyl)pyrrolidine (Compd. No. 1896) (9.1 mg, 38%). The purity was determined by RPLC/MS (93%). ESI/ MS m/e 483 (M++H, C₂₂H₂₅F₃N₄O₅).

[Examples 750 to 757]

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[0157] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 749. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 10.

Table 10

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
750	1897	C ₂₂ H ₂₅ F ₃ N ₄ O ₃ S	483	22.7	94.1
751	1898	C ₂₃ H ₂₇ F ₃ N ₄ O ₃	465	12.2	52.5
752	1899	C ₂₄ H ₂₉ F ₃ N ₄ O ₃	479	14.4	60.2
753	1900	C ₂₂ H ₂₅ F ₃ N ₄ O ₅	483	2.6	10.8
754	1901	C ₂₄ H ₂₉ F ₃ N ₄ O ₃	479	14.5	60.6
755	1902	C ₂₃ H ₂₅ F ₃ N ₄ O ₄	479	12.0	50.2
756	1915	C ₂₃ H ₂₇ F ₃ N ₄ O ₅	467.2	2.5	6.7
757	1916	C ₂₂ H ₂₅ F ₃ N ₄ O ₄	467.2	3.1	8.9

[Example 758] Synthesis of (R)-3-[[N-(2-amino-5-trifluoromethyl)benzoyl]glycyl]amino]-1-(4-vinylbenzyl)pyrrolidine (Compd. No. 1701)

[0158] A mixture of (R)-3-[[N-(2-amino-5-(trifluoromethyl)benzoyl)glycyl]amino]pyrrolidine (0.050 mmol) with 4-vinyl-benzyl chloride (9.9 mg, 0.065 mL), a piperidinopolystyrene (60 mg), acetonitrile (1.0 mL) and chloroform (0.30 mL) was stirred at 50 °C for 12 hours. The resulting reaction mixture was cooled to room temperature, loaded onto a VarianTM SCX column and washed with methanol (15 mL). The obtained crude product was eluted with solution of 2 M NH₃ in a methanol (5 mL) and concentrated to thereby afford (R)-3-[[N-(2-amino-5-(trifluoromethyl)benzoyl)glycyl]

amino]-1-(4-vinylbenzyl)pyrrolidine (Compd. No. 1701) (19.6 mg, 88%). The purity was determined by RPLC/MS (92%). ESI/MS m/e 547.2 (M++H, $C_{23}H_{25}CIF_3N_4O_2$).

[Examples 759 to 762]

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[0159] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 758. The obtained products, if necessary, were purified with preparative TLC to provide the objective substances. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 11.

Table 11

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
759	1702	$C_{22}H_{25}F_3N_4O_3$	451.2	5.3	24
760	1703	C ₂₂ H ₂₃ F ₃ N ₄ O ₄	465.2	5.0	22
761	1704	C ₂₁ H ₂₃ F ₃ N ₄ O ₃	437.2	20.9	96
762	1705	C ₂₁ H ₂₁ Cl ₂ F ₃ N ₄ O ₂	489.2	9.3	38

[Example 763] Synthesis of (R)-3-[[N-(2-amino-5-(trifluoromethoxy)benzoyl)glycyl]amino-1-(2,4-dichlorobenzyl) pyrrolidine (Compd. No. 1905)

[0160] A mixture of (R)-3-[[N-(2-amino-5-(trifluoromethoxy)benzoyl)glycyl]amino]pyrrolidine (0.050 mmol) with 2,4-dichlorobenzyl chloride (0.066 mL), a piperidinomethylpolystyrene (60 mg), acetonitrile (0.8 mL) and chloroform (0.5 mL) was stirred at 60 °C for 12 hours. The resulting reaction mixture was cooled to room temperature, loaded onto a Varian™ SCX column and washed with a 50% chloroform/methanol (10 mL) and methanol (10 mL). The obtained crude product was eluted with a solution of 2 M NH₃ in methanol (5 mL) and concentrated. A 1,4-dioxane (2 mL) solution of 4 M HCl was added to the resulting residue, and the obtained mixture was stirred at room temperature overnight, concentrated and then purified by preparative TLC to afford (R)-3-[[N-(2-amino-5-(trifluoromethoxy]benzoyl]glycyl]amino]-1-(2,4-dichlorobenzyl)pyrrolidine (Compd. No. 1905) (17.6 mg, 70%). The purity was determined by RPLC/MS (93%). ESI/MS m/e 505 (M++H, C₂₁H₂₁Cl₂F₃N₄O₃).

[Examples 764 to 770]

[0161] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 763. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 12.

Table 12

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
764	1906	C ₂₂ H ₂₃ F ₃ N ₄ O ₅	481	9.4	39.1
765	1907	C ₂₁ H ₂₃ F ₃ N ₄ O ₄	453	7.5	33.2
766	1908	C ₂₂ H ₂₅ F ₃ N ₄ O ₄	467	7.7	33.0
767	2180	C ₂₂ H ₂₄ CIF ₃ N ₄ O ₂	469	1.3	26
768	2181	C ₂₃ H ₂₅ F ₃ N ₆ O ₃	491	4.3	52
769	2182	C ₁₉ H ₂₂ F ₃ N ₅ O ₂ S	442	7.0	51
770	1909	C ₂₃ H ₂₅ F ₃ N ₄ O ₃	463	8.7	37.6

[Example 771] Synthesis of (R)-3-[[N-(2-amino-5-trifluoromethoxybenzoyl)glycyl]amino]-1-(2-amino-4-chlorobenzyl) pyrrolidine (Compd. No. 1921)

[0162] A mixture of (R)-3-[[N-(2-amino-5-trifluoromethoxybenzoyl)glycyl]amino]pyrrolidine (0.050 mmol) with 4-chloro-co-2-nitrobenzyl chloride (0.050 mmol), a piperidinomethylpolystyrene (60 ing), acetonitrile (1.0 mL) and chloroform (0.7 mL) was stirred at 50 °C overnight. The resulting reaction mixture was cooled, loaded onto a Varian™ SCX column

and washed with 50% chloroform/methanol (10 mL) and methanol (10 mL). The obtained crude product was eluted with a solution of 2 M NH3 in methanol (5 mL) and concentrated. Ethanol (3 mL) and 10% palladium carbon were added to the resulting residue, and the solution was stirred at room temperature under a hydrogen atmosphere for 1.5 hours. The obtained solution was filtered, concentrated and then purified by preparative TLC to thereby provide (R)-3-[[N-(2-amino-5-trifluoromethoxybenzoyl)glycyl]amino]-1-(2-amino- 4-chlorobenzyl)pyrrolidine (Compd. No. 1921) (2.2 mg, 6%). The purity was determined by RPLC/MS (81%). ESI/MS m/e 486.2 (M++H, C₂₁H₂₃CIF₃N₅O₃).

[Example 772] Synthesis of (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4-bromo-2-fluorobenzyl) pyrrolidine (Compd. No. 2120)

[0163] A methanol (0.50 mL) solution of NaBH₃CN (0.25 mmol) was added to a mixture of (R)-3-[[N-(2-tert-butoxy-carbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (0.050 mmol) with 4-bromo-2-fluorobenzaldehyde (0.015 mmol), methanol (1.5 mL) and acetic acid (0.016 mL). The resulting reaction mixture was stirred at 50 °C overnight, cooled to room temperature, then loaded onto a VarianTM SCX column and washed with methanol (5 mL×2). The obtained product was eluted with a solution of 2 M NH₃ in methanol (5 mL) and concentrated. The resulting residue was dissolved in methanol (0.25 mL), and a dioxane solution of 4 M HCl was added to the obtained solution. The resulting solution was stirred at room temperature for 5 hours and concentrated. The obtained residue was dissolved in methanol, loaded onto a VarianTM SCX column and washed with methanol (5 mL×2). The resulting crude product was eluted with a solution of 2 M NH₃ in methanol (5 mL) and concentrated. The obtained residue was dissolved in ethyl acetate (0.5 mL), loaded onto a VarianTM SCX column, eluted with ethyl acetate/methanol = 5:1 (6 mL) and concentrated to thereby afford (R)-3-[[N- (2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4-bromo-2-fluorobenzyl) pyrrolidine (Compd. No. 2120) (16.0 mg, 31%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 517.0 (M++H, C₂₁H₂₁BrF₄N₄O₂).

[Examples 773 to 793]

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[0164] The compounds used in the present invention were synthesized by using the respective starting materials and reactants according to the method of Example 772. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 13.

Table 13

Example	Compd. No.	Molecular Formula	EMI/MS me	Yield (mg)	Yield (%)
773	2083	C ₂₂ H ₂₄ BrF ₃ N ₄ O ₄	545.2	2.9	11
774	2084	C ₂₃ H ₂₇ F ₃ N ₄ O ₅	497.2	5.1	21
775	2085	C ₂₂ H ₂₅ F ₃ N ₄ O ₄	467.2	3.1	13
776	2086	C ₂₁ H ₂₂ CIF ₃ N ₄ O ₃	471.0	4.6	20
777	2087	$C_{23}H_{28}F_3N_5O_2$	464.2	5.6	24
778	2088	$C_{25}H_{32}F_3N_5O_2$	492.2	5.9	24
779	2089	$C_{21}H_{21}F_5N_4O_2$	457.2	4.5	20
780	2090	$C_{27}H_{27}F_3N_4O_3$	513.2	8.0	31
781	2118	C ₂₁ H ₂₃ F ₃ N ₄ O ₄	453.1	2.7	12
782	2119	$C_{21}H_{23}F_3N_4O_4$	453.1	4.3	19
783	2121	$C_{22}H_{25}F_3N_4O_4$	467.0	1.2	2
784	2122	C ₂₁ H ₂₁ ClF ₄ N ₄ O ₂	472.9	13.1	28
785	2123	$C_{22}H_{22}F_3N_5O_6$	510.1	13.1	51
786	2124	C ₂₁ H ₂₁ CIF ₃ N ₅ O ₄	500.1	15.6	62
787	2125	$C_{22}H_{24}F_3N_5O_5$	496.0	16.0	65
788	2126	$C_{22}H_{24}F_3N_5O_4$	480.1	15.6	65
789	2137	C ₂₂ H ₂₄ CIF ₃ N ₄ O ₂	469.2	2.6	11

Table 13 (continued)

Example	Compd. No.	Molecular Formula	EMI/MS me	Yield (mg)	Yield (%)
790	2138	$C_{26}H_{29}F_3N_6O_2$	515.3	25.1	98
791	2139	C ₂₀ H ₂₄ CIF ₃ N ₆ O ₂	473.2	25.0	98
792	2149	C ₂₁ H ₂₂ F ₃ N ₅ O ₅	482.3	4.9	34
793	2157	C ₂₂ H ₂₅ F ₃ N ₄ O ₃	451.2	15.5	70

[Example 794] Synthesis of (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1(2,4-dimethoxypyrimidin-5-ylmethyl)pyrrolidine (Compd. No. 2175)

[0165] (R)-3-[[N-(2-Amino-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (17.2 mg, 0.04 mmol) was dissolved in THF (1 mL), and 2,4-dimethoxy-5-pyrimidinecarboxaldehyde (6.7 mg, 0.04 mmol) was added to the resulting solution. Sodium triacetoxyborohydride (12.7 mg, 0.06 mmol) and glacial acetic acid (2.4 mg, 0.04 mmol) were subsequently added to the mixture. The resulting mixture was stirred at 50 °C for 24 hours and then concentrated. The residue was dissolved in dichloromethane (1 mL) and washed with a 1 M aqueous solution (1 mL) of NaOH. The organic layer was collected and concentrated, and a dichloromethane solution of 25% trifluoroacetic acid (1 mL) was added. The resulting mixture was stirred at room temperature for 1 hour and then concentrated. The obtained residue was purified by HPLC to thereby provide (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(2,4-dimethoxypyrimidin-5-ylmethyl) pyrrolidine (Compd. No. 2175) (18.6 mg, 78%). The purity was determined by RPLC/MS (98%). ESI/MS m/e 483 (M*+H, C₂₁H₂₅F₃N₆O₄).

[Examples 795 to 803]

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[0166] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according the method of Example 794. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 14.

Table 14

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
795	2165	C ₁₈ H ₂₁ F ₃ N ₆ O ₂	411	2.0	27
796	2166	C ₁₈ H ₂₀ F ₃ N ₅ O ₂ S	428	9.9	66
797	2167	C ₂₄ H ₂₅ F ₃ N ₆ O ₂	487	15.1	73
798	2169	C ₂₄ H ₂₉ F ₃ N ₄ O ₂	463	1.2	24
799	2170	C ₂₆ H ₂₅ CIF ₃ N ₅ O ₂	520	6.0	40
800	2171	C ₁₉ H ₂₃ F ₃ N ₆ O ₂	425	16.8	88
801	2174	$C_{23}H_{24}BrF_3N_4O_2S_2$	591	5.3	53
802	2178	C ₂₅ H ₂₈ F ₃ N ₅ O ₄	518	5.4	62
803	2179	C ₂₅ H ₂₈ F ₃ N ₅ O ₃	502	6.3	60

[Example 804] Synthesis of (R)-1-(2-amino-4,5-methylenedioxybenzyl)-3-[[N-(2-amino-5-trifluoromethylbenzoyl) glycyl]amino]pyrrolidine (Compd. No. 2127)

[0167] A mixture of (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4,5-methylenedioxy-2-nitrobenzyl) pyrrolidine (30.5 mg) with 10% Pd carbon (6 mg) and methanol (3 mL) was stirred at room temperature under a hydrogen atmosphere for 10 hours. The palladium catalyst was filtered through Celite, and the filtrate was concentrated and purified by solid-phase extraction (Bond ElutTM SI, 20% methanol/ethyl acetate) to thereby afford (R)-1-(2-amino-4,5-methylenedioxybenzyl)-3-[[N-2-amino-5-trifluoromethylbenzoyl]glycyl]amino]pyrrolidine (Compd. No. 2127) (21.9 mg, 76%). The purity was determined by RPLC/MS (95%). ESI/MS m/e 480.1 (M++H, C₂₂H₂₄F₃N₅O₄).

[Examples 805 to 806]

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[0168] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 804. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 15.

Table 15

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
805	2128	C ₂₂ H ₂₆ F ₃ N ₅ O ₃	466.0	8.6	30
806	2129	C ₂₂ H ₂₆ F ₃ N ₅ O ₂	450.1	13.1	37

[Example 807] Synthesis of (R)-1-(3-amino-4-chlorobenzyl)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino] pyrrolidine (Compd. No. 2132)

[0169] A mixture of (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4-chloro-3-nitrobenzyl)pyrrolidine (32.6 mg) with 10% palladium carbon (8 mg), ethyl acetate (2.7 mL) and methanol (0.3 mL) was stirred at room temperature under a hydrogen atmosphere for 15 hours. The palladium carbon was removed by filtration, and the filtrate was concentrated and purified by solid-phase extraction (Bond Elut™ SI, 20% methanol/ethyl acetate) to thereby provide (R)-1-(3-amino-4-chlorobenzyl)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 2132) (10.5 mg, 34%). The purity was determined by RPLC/MS (84%). ESI/MS m/e 470.2 (M++H, C₂₁H₂₃F₃N₅O₂).

[Example 808] Synthesis of (R)-1-(2-amino-4,5-methylenedioxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine

[0170] A methanol (1.50 mL) solution of NaBH₃CN (0.75 mmol) was added to a mixture of (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (0.150 mmol) with 4,5-methylenedioxy-2-nitrobenzaldehyde (0.45 mmol), methanol (4.5 mL) and acetic acid (0.048 mL). The resulting reaction mixture was stirred at 50 °C overnight, cooled to room temperature, loaded onto a VarianTM SCX column and washed with methanol. The obtained crude product was eluted with a 2 M methanol solution of NH₃ and concentrated to thereby afford (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4,5-methylenedioxy-2-nitrobenzyl)pyrrolidine.

[0171] A mixture of the resulting (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4,5-methylenedioxy-2-nitrobenzyl)pyrrolidine (0.150 mmol) with 10% Pd carbon (22 mg) and methanol (4.5 mL) was stirred at room temperature under a hydrogen atmosphere overnight. The palladium catalyst was removed by filtration, and the filtrate was concentrated to thereby afford (R)-1-(2-amino-4,5-methylenedioxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (87.1 mg, quantitative). Any noticeable by-product was not detected in TLC.

[0172] Further, (R)-1-(3-amino-4-methoxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine and (R)-1-(3-amino-4-methylbenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 808.

[0173] (R)-1-(3-amino-4-methoxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine: 101 mg, quantitative. Any noticeable by-product was not detected in TLC.

[0174] (R)-1-(3-amino-4-methylbenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino] pyrrolidine: 97.2 mg, quantitative. Any noticeable by-product was not detected in TLC.

[Example 809] Synthesis of (R)-1-(3-amino-4-chlorobenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine

[0175] A methanol (1.50 mL) solution of NaBH₃CN (0.75 mmol) was added to a mixture of (R)-3-[[N-(2-(tert-butox-ycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (0.150 mmol) with 4-chloro-3-nitrobenzaldehyde (0.45 mmol), methanol (4.5 mL) and acetic acid (0.048 mL). The resulting reaction mixture was then stirred at 50 °C overnight, cooled to room temperature, loaded onto a VarianTM SCX column and washed with methanol. The obtained product was eluted with a 2 M methanol solution of NH₃ and concentrated to thereby provide (R)-3-[[N-(2-(tert-butox-ycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4-chloro-3-nitrobenzyl)pyrrolidine.

[0176] A mixture of the resulting (R)-3-[N-(2-tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]-1-(4-

chloro-3-nitrobenzyl)pyrrolidine with 10% Pd carbon (22 mg), ethyl acetate (2.7 mL) and methanol (0.3 mL) was stirred at room temperature under a hydrogen atmosphere for 15 hours. The palladium catalyst was removed by filtration, and the filtrate was concentrated to afford (R)-1-(3 -amino-4-chlorobenzyl)-3-[[N-(2-tert-butoxycarbonylamino)-5-trif-luoromethylbenzoyl]glycyl]amino]pyrrolidine (89.7 mg, quantitative). Any noticeable by-product was not detected in TLC.

[Example 810] Synthesis of (R)-1-(3-amino-4-hydroxybenzyl)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino] pyrrolidine (Compd. No. 2187)

[0177] A 4 M HCl dioxane (2.0 mL) solution of (R)-1-(3-amino-4-hydroxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (20 mg) synthesized according to the method of Example 808 was stirred at room temperature overnight. The solution was concentrated, and the residue was then dissolved in methanol, loaded onto a Varian™ SCX column, washed with methanol, subsequently eluted with a 2 M methanol solution of NH₃, concentrated and then purified by preparative TLC (SiO₂, ethyl acetate/methanol = 4:1) to thereby provide (R)-1-(3-amino-4-hydroxybenzyl)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 2187) (9.6 mg, 59%). The purity was determined by RPLC/MS (86%). ESI/MS m/e 452.3 (M++H, C₂₁H₂₄F₃N₅O₃).

[Example 811] Synthesis of (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-[4-chloro-3-(dimethylamino) benzyl]pyrrolidine (Compd. No. 2133)

[0178] NaBH3CN (38 mg) was added to a mixture of (R)-1-(3-amino-4-chlorobenzyl)-3-[[N-(2-tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl]glycyl]amino]pyrrolidine (44.9 mg) with methanol (0.95 mL), acetic acid (0.05 mL) and a 37% aqueous solution of HCHO (0.15 mL). The resulting reaction mixture was stirred at 50 °C overnight, cooled to room temperature and concentrated. A 2 M aqueous solution of NaOH and ethyl acetate were then added to the residue to separate the organic layer. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried and concentrated. The residue was loaded onto a Varian™ SCX column and washed with methanol. The resulting product was eluted with a 2 M methanol solution of NH₃ and concentrated. The residue was dissolved in a 50% concentrated hydrochloric acid/dioxane and stirred at room temperature for 1 hour. The reaction solution was adjusted to pH 10 with a 5 M aqueous solution of NaOH and extracted with ethyl acetate (twice). The extracts were combined, dried over Na₂SO₄, filtered, concentrated and purified by preparative TLC (SiO₂, 20% methanol/ethyl acetate) to thereby afford (R)-3-[[N-2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-[4-chloro-3-(dimethylamino)benzyl] pyrrolidine (Compd. No. 2133) (10.9 mg, 28%). The purity was determined by RPLC/MS (95%). ESI/MS m/e 498.3 (M*+H, C₂₃H₂₇CIF₃N₅O₂).

[Examples 812 to 814]

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[0179] The compounds used in the present invention were synthesized by using the respective starting materials and reactants according to the method of Example 811. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 16.

Table 16

Example	Comps. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
812	2134	C ₂₄ H ₂₈ F ₃ N ₅ O ₄	508.4	19.0	50
813	2135	C ₂₄ H ₃₀ F ₃ N ₅ O ₃	494.4	21.8	50
814	2136	C ₂₄ H ₃₀ F ₃ N ₅ O ₂	478.4	29.2	69

[Example 815] Synthesis of (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(3-methylamino-4-hydroxybenzyl)pyrrolidine (Compd. No. 2158)

[0180] NaBH₃CN (9.2 mg) was added to a mixture of (R)-1-(3-amino-4-hydroxybenzyl)-3-[[N-(2-(tert-butoxycarbo-nylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (27.3 mg, 0.049 mmol) with a 37% HCHO solution (4.0 mg, 0.049 mmol), acetic acid (0.10 mL) and methanol (1.3 mL). The resulting reaction mixture was stirred at 60 °C overnight, cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol (5 mL × 2). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (8 mL) and concentrated.

[0181] The resulting residue was dissolved in methanol (1 mL), and a 4 M dioxane solution of HCl (1.0 mL) was added to the solution. The resulting mixture was stirred at room temperature for 3 hours and concentrated. The residue

was dissolved in methanol (1 mL), loaded onto a Varian[™] column, washed with methanol (5 mL × 2), eluted with a 2 M methanol solution of NH₃ (8 mL), concentrated and then purified by preparative TLC (SiO₂) to thereby provide (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(3-methylamino-4-hydroxybenzyl)pyrrolidine (Compd. No. 2158) (4.3 mg, 19%). The purity was determined by RPLC/MS (71%). ESI/MS m/e 480.3 (M++H, C₂₂H₂₆F₃N₅O₃).

[Example 816] Synthesis of (R)-1-(3-acetylamino-4-methoxybenzyl)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl] amino]pyrrolidine (Compd. No. 2152)

[0182] Acetic anhydride (1 mL) was added to a pyridine (1 mL) solution of (R)-1-(3-amino-4-hydroxybenzyl)-3-[[N-(2-(tert butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (50.5 mg). The resulting reaction mixture was stirred at room temperature overnight, and methanol was added to the mixture. The obtained mixture was concentrated, and a 1 M NaOH solution was then added to the concentrate. The resulting mixture was extracted with ethyl acetate, and the organic layer was concentrated and purified by preparative TLC (SiO₂) to thereby afford (R)-1-(3-acetylamino-4-methoxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine.

[0183] The resulting (R)-1-(3-acetylamino-4-methoxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine was dissolved in a 50% dioxane solution of 6 M hydrochloric acid, and the obtained solution was stirred at room temperature for 2 hours, adjusted to pH 10 with a 5 M NaOH solution and extracted with ethyl acetate. The organic layer was concentrated and purified by preparative TLC (SiO₂) to thereby provide (R)-1-(3-acetylamino-4-methoxybenzyl)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]pyrrolidine (Compd. No. 2152) (3.7 mg, 8%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 508.3 (M++H, C₂₄H₂₈F₃N₅O₄).

[Examples 817 to 819]

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[0184] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 816. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 17.

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
817	2150	C ₂₃ H ₂₅ CIF ₃ N ₅ O ₃	512.3	3.8	9
818	2151	C ₂₄ H ₂₆ F ₃ N ₅ O ₅	522.2	3.1	8
819	2153	C24H28F3N5O3	492.3	4.3	10

Table 17

[Example 820] Synthesis of (R)-3-[[N(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(benz[d]oxazol-5-yl) pyrrolidine (Compd. No. 2189)

[0185] Triethyl orthoformate (0.20 mL, 3.3 equivalents) and pyridinium p-toluenesulfonate (1.2 mg, 0.4 equivalent) were added to a THF (2 mL). solution of (R)-1-(3-amino-4-hydroxybenzyl)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trif-luoromethylbenzoyl)glycyl]amino]pyrrolidine (20 mg) synthesized according to the method of Example 808. The resulting reaction mixture was stirred at room temperature overnight under reflux. The reaction mixture was cooled to room temperature and then concentrated. The obtained residue was dissolved in ethyl acetate, loaded onto a Bond ElutTM Si column, eluted with ethyl acetate/methanol = 4:1 and concentrated.

[0186] The resulting residue was dissolved in ethyl acetate (1.5 mL), and a 4 M dioxane solution of HCl was added to the obtained solution. The resulting solution was stirred overnight, adjusted to pH 10 with a 5 M aqueous solution of NaOH and extracted with ethyl acetate. The obtained extract was concentrated and purified by preparative TLC (SiO₂, ethyl acetate/methanol = 4:1) to thereby provide (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-(benz[d]oxazol-5-yl)pyrrolidine (Compd. No. 2189) (0.5 mg, 3%). The purity was determined by RPLC/MS (97%). ESI/MS m/e 462.3 (M*+H, $C_{22}H_{22}F_3N_5O_3$).

[Example 821] Synthesis of (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyt]amino]-1-[benzo[c]thiadiazol-5-yl] pyrrolidine (Compd. No. 2183)

[0187] Methanesulfonyl chloride (0.0042 mL) was added to a mixture of 5-(hydroxymethyl)benzo[c]thiadiazole (8.3 mg, 0.050 mmol) with a (piperidinomethyl)polystyrene (86 mg) and chloroform (1 mL). The resulting mixture was stirred at room temperature for 1.5 hours. Acetonitrile (1 ml) and (R)-3-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethyl-

benzyl)glycyl]amino]pyrrolidine (0.060 mmol) were added to the mixture. The resulting mixture was stirred at 50°C for 3 hours. After cooling to room temperature, phenyl isocyanate (30 mg) was added, and the obtained mixture was stirred at room temperature for 1 hour, loaded onto a VarianTM SCX column and washed with methanol (5 mL) and chloroform (5 mL). The resulting crude product was eluted with a 2 M methanol solution of NH₃ (3 mL) and concentrated.

[0188] The obtained substance was dissolved in dichloromethane (1 mL), and a dichloromethane solution (1 mL) of 1 M chlorotrimethylsilane (1 M) and phenol (1 M) was added to the solution. The resulting solution was stirred at room temperature for 5 hours, loaded onto a VarianTM SCX column and washed with methanol and dichloromethane. The obtained product was eluted with a 2 M methanol solution of NH₃ and concentrated.

[0189] The resulting crude product was purified by preparative TLC (SiO_2 , ethyl acetate/methanol = 3:1) to thereby afford (R)-3-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]amino]-1-[benzo[c]thiadiazol-5-yl]pyrrolidine (Compd. No. 2183) (11.5 mg, 58%). The purity was determined by RPLC/MS (86%). ESI/MS m/e 479.2 (M+H, $C_{21}H_{21}F_3N_6O_2S$).

[Reference Example 6] Synthesis of 4-[[N-(1-(9-fluorenylmethoxycarbonyl)pyrrolidin-3-yl)carbamoylmethyl] amimomethyl]3-methoxyphenyloxymethyl-polystyrene

[0190] Acetic acid (0.3 mL), sodium triacetoxyborohydride (1.92 g) and a 4-formyl- 3-(methoxyphenyloxymethyl)-polystyrene (1 mmol/g, 200 g) were added to a DMF (65 mL) solution of (R)-1-(9-fluorenylmethoxycarbonyl)-3-gly-cylaminopyrrolidine hydrochloride (4.38 g, 10 mmol). The resulting mixture was shaken for 2 hours and then filtered. The resin was washed with methanol, DMF, dichloromethane and methanol and dried to thereby provide the objective substance (2.73 g).

[Examples 822 to 912] Solid-phase synthesis of 3-aminopyrrolidines

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[0191] Diisopropylethylamine (3.6 mL) was added to a mixture of the corresponding carboxylic acid (1.6 mmol) with HBTU (1.6 mmol) and DMF (6 mL), and the resulting mixture was shaken for 2 minutes. A 4-[[N-(1-(9-fluorenylmethox-ycarbonyl)pyrrolidin-3-yl)carbamoylmethyl]aminomethyl]-3-methoxyphenyloxymethyl-polystyrene (400 mg, 0.4 mmol) was added, and the obtained mixture was shaken for 1 hour and then filtered. The resin was washed with DMF and dichloromethane and dried.

[0192] A mixture of the resulting resin with piperidine (3.2 mL) and DMF (12.8 mL) was shaken for 10 minutes and then filtered. The resin was washed with DMF and dichloromethane and dried.

[0193] A mixture of NaBH(OAc)₃ (0.25 mmol) with acetic acid (0.025 mL) and DMF (1 mL) was added to the dried resin (0.05 mL). The corresponding aldehyde (2.5 mmol) was added, and the mixture was shaken for 2 hours, then filtered and washed with methanol, a 10% solution of disopropylethylamine in DMF, DMF, dichloromethane and methanol. A mixture of the resin with water (0.050 mL) and trifluoroacetic acid (0.95 mL) was shaken for 1 hour and then filtered. The resin was washed with dichloromethane and methanol. The filtrate and washings were combined and concentrated. The resulting crude product was loaded onto a VarianTM SCX column and washed with methanol (15 mL). The product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated.

[0194] The obtained products, if necessary, were purified with preparative TLC or HPLC to thereby afford the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 18.

Table 18

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
822	1805	$C_{21}H_{21}BrF_3N_3O_2S$	516	13.3	76
823	1806	C ₂₂ H ₂₄ F ₃ N ₃ O ₃ S	468	12.8	81
824	1807	$C_{22}H_{24}F_3N_3O_4S$	484	13.7	83
825	1808	C ₂₂ H ₂₄ F ₃ N ₃ O ₄ S	484	14.9	91
826	1809	C ₂₁ H ₂₂ F ₃ N ₃ O ₃ S	454	12.9	84
827	1810	C ₂₂ H ₂₂ F ₃ N ₃ O ₄ S	482	12.9	79
828	1811	$C_{24}H_{26}F_3N_3O_2S$	478	12.9	79
829	1812	C ₂₂ H ₂₄ F ₃ N ₃ O ₂ S ₂	484	5.3	32
830	1813	$C_{23}H_{26}F_3N_3O_2S$	466	12.8	81
831	1814	$C_{23}H_{24}F_3N_3O_3S$	480	9.7	59

Table 18 (continued)

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	Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
	832	1815	C ₂₃ H ₂₆ F ₃ N ₃ O ₂ S	466	12.7	80
	833	1816	C ₂₄ H ₂₈ F ₃ N ₃ O ₂ S	480	14.4	88
	834	1817	C ₂₅ H ₃₀ F ₃ N ₃ O ₂ S	494	14.1	84
	835	1818	C ₂₁ H ₂₂ BrF ₂ N ₃ O ₃	482	13.4	82
	836	1819	C ₂₂ H ₂₅ F ₂ N ₃ O ₄	434	11.7	79
	837	1820	$C_{22}H_{25}F_2N_3O_5$	450	11.8	77
	838	1821	$C_{22}H_{25}F_2N_3O_5$	450	13.3	87
	839	1822	C ₂₁ H ₂₃ F ₂ N ₃ O ₄	420	11.9	83
	840	1823	C ₂₂ H ₂₃ F ₂ N ₃ O ₅	448	11.9	78
	841	1824	C ₂₄ H ₂₇ F ₂ N ₃ O ₃	444	9.1	60
	842	1825	C ₂₂ H ₂₅ F ₂ N ₃ O ₃ S	450	11.3	74
	843	1826	C ₂₃ H ₂₇ F ₂ N ₃ O ₃	432	10.8	74
	844	1827	C ₂₃ H ₂₅ F ₂ N ₃ O ₄	446	12.7	84
	845	1828	C ₂₃ H ₂₇ F ₂ N ₃ O ₃	432	11.7	80
•	846	1829	C ₂₄ H ₂₉ F ₂ N ₃ O ₃	446	14.3	94
	847	1830	C ₂₄ H ₂₉ F ₂ N ₃ O ₃	446	10.0	66
	848	1831	C ₂₂ H ₂₈ BrN ₃ O ₃	462	4.8	31
	849	1832	C ₂₃ H ₃₁ N ₃ O ₄	414	10.4	74
	850	1833	C ₂₃ H ₃₁ N ₃ O ₅	430	12.1	83
	851	1834	C ₂₃ H ₃₁ N ₃ O ₅	430	12.0	82
	852	1835	C ₂₂ H ₂₉ N ₃ O ₄	400	7.9	58
	853	1836	C ₂₃ H ₂₉ N ₃ O ₅	428	11.1	76
	854	1837	C ₂₅ H ₃₃ N ₃ O ₃	424	13.3	92
	855	1838	C ₂₃ H ₃₁ N ₃ O ₃ S	430	8.7	60
-	856	1839	C ₂₄ H ₃₃ N ₃ O ₃	412	11.3	81
	857	1840	C ₂₄ H ₃₁ N ₃ O ₄	426	12.9	89
	858	1841	C ₂₄ H ₃₃ N ₃ O ₃	413	12.8	91
	859	1842	C ₂₅ H ₃₅ N ₃ O ₃	426	8.7	60
	860	1843	C ₂₅ H ₃₅ N ₃ O ₃	426	12.2	84
	861	1844	C ₂₆ H ₃₇ N ₃ O ₃	440	11.3	76
	862	1845	C ₃₁ H ₃₇ BrN ₄ O ₂	577	6.4	30
	863	1846	C ₂₃ H ₂₈ F ₃ N ₃ O ₂ S	480	12.8	81
	864	1847	C ₂₅ H ₃₁ F ₂ N ₃ O ₃	460	12.2	78
	865	1848	C ₂₇ H ₂₉ N ₃ O ₄	460	6.1	39
	866	1849	C ₂₉ H ₃₁ N ₃ O ₂	454	15.1	98
	867	1850	C ₂₈ H ₃₁ N ₃ O ₂	. 442	12.7	85
	868	1851	C ₂₈ H ₃₁ N ₃ O ₂	442	14.3	95
	869	1852	C ₂₈ H ₂₉ N ₃ O ₃	456	3.4	22
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Table 18 (continued)

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		Table 16 (COTIL	in aca)		
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
870	1853	C ₂₇ H ₂₉ N ₃ O ₆ S	524	15.4	87
871	1854	C ₂₉ H ₃₁ N ₃ O ₄ S	518	15.8	90
872	1855	C ₂₈ H ₃₁ N ₃ O ₄ S	506	17.0	99
873	1856	C ₂₈ H ₃₁ N ₃ O ₄ S	506	3.0	17
874	1857	C ₂₈ H ₂₉ N ₃ O ₅ S	520	10.0	57
875	1858	C ₂₀ H ₂₂ Br ₂ N ₄ O ₂	511	9.3*	37
876	1859	C ₂₁ H ₂₅ BrN ₄ O ₃	461	6.7*	29
877	1860	C ₂₁ H ₂₅ BrN ₄ O ₄	477	9.5*	40
878	1861	C ₂₁ H ₂₅ BrN ₄ O ₄	477	10.0*	42
879	1862	C ₂₀ H ₂₃ BrN ₄ O ₃	447	7.8*	34
880	1863	C ₂₁ H ₂₃ BrN ₄ O ₄	475	3.4*	14
881	1864	C ₂₁ H ₂₅ BrN ₄ O ₂ S	477	3.9*	16
882	1865	C ₂₂ H ₂₅ BrN ₄ O ₃	473	6.4*	27
883	1866	C ₂₃ H ₂₉ BrN ₄ O ₂	472	7.0*	29
884	1867	C ₂₃ H ₂₉ BrN ₄ O ₂	473	7.6*	32
885	1868	C ₂₄ H ₃₁ BrN ₄ O ₂	487	9.1*	37
886	1869	C ₂₀ H ₂₂ BrlN ₄ O ₂	557	8.9*	33
887	1870	C ₂₁ H ₂₅ IN ₄ O ₃	509	9.2*	37
888	1871	C ₂₁ H ₂₅ IN ₄ O ₄	525	6.3*	25
889	1872	C ₂₁ H ₂₅ IN ₄ O ₄	525	5.9*	23
890	1873	C ₂₀ H ₂₃ IN ₄ O ₃	495	7.7*	31
891	1874	C ₂₁ H ₂₃ IN ₄ O ₄	523	8.2*	32
892	1875	C ₂₃ H ₂₇ IN ₄ O ₂	519	6.7*	26
893	1876	C ₂₁ H ₂₅ IN ₄ O ₂	525	4.3*	17
894	1877	C ₂₂ H ₂₇ IN ₄ O ₂	507	7.9*	32
895	1878	C ₂₂ H ₂₅ IN ₄ O ₃	521	8.4*	33
896	1879	C ₂₃ H ₂₉ IN ₄ O ₂	521	8.2*	32
897	1880	C ₂₃ H ₂₉ IN ₄ O ₂	521	8.1*	32
898	1881	C ₂₄ H ₃₁ IN ₄ O ₂	535	8.6*	33
899	1882	C ₂₀ H ₂₂ BrN ₅ O ₄	476	5.3*	22
900	1883	C ₂₁ H ₂₅ N ₅ O ₅	428	5.7*	26
901	1884	C ₂₁ H ₂₅ N ₅ O ₆	444	. 8.2*	36
902	1885	C ₂₁ H ₂₅ N ₅ O ₆	444	5.0*	22
903	1886	C ₂₀ H ₂₃ N ₅ O ₅	414	8.7*	40
904	1887	C ₂₁ H ₂₃ N ₅ O ₆	442	7.8*	34
905	1888	C ₂₃ H ₂₇ N ₅ O ₄	438	5.6*	25
906	1889	C ₂₁ H ₂₅ N ₅ O ₄ S	444	13.2*	58
907	1890	C ₂₂ H ₂₇ N ₅ O ₄	426	11.3*	51

Table 18 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)			
908	1891	C ₂₂ H ₂₅ N ₅ O ₅	440	7.4*	33			
909	1892	C ₂₂ H ₂₇ N ₅ O ₄	426	5.5*	25			
910	1893	C ₂₃ H ₂₉ N ₅ O ₄	440	5.7*	25			
911	1894	C ₂₃ H ₂₉ N ₅ O ₄	440	9.4*	41			
912	1895	C ₂₄ H ₃₁ N ₅ O ₄	455	8.5*	37			
Note:	Note: * indicates "yield (mg) of trifluoroacetate".							

[Reference Example 7] Synthesis of 2-carbamoyl-1-(4-chlorobenzyl)pyrrolidine

[0195] Triethylamine (7.45 mL) and 4-chlorobenzyl chloride (3.88 g, 24.1 mmol) were added to an acetonitrile (35 mL) solution of d1-prolinamide hydrochloride (2.5 g, 21.8 mmol). The resulting reaction mixture was stirred at 70°C for 4 hours and subsequently stirred at 25 °C for 16 hours. The resulting mixture was diluted with dichloromethane (20 mL) and washed with water (30 mL×3). The organic layer was dried (over MgSO₄) and concentrated. The obtained crude product was purified by chromatography (SiO₂, methanol-dichloromethane) to thereby provide 2-carbamoyl-1-(4-chlorobenzyl)pyrrolidine (5.21 g, 81%).

[Reference Example 8] Synthesis of 2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine

[0196] 2-Carbamoyl-1-(4-chlorobenzyl)pyrrolidine was dissolved in 1 M BH₃-THF (9.4 mL), and the resulting solution was heated at 70 °C. A 1 M BH₃-THF (0.5 equivalent) was further added twice after 16 hours and 25 hours. After 40 hours, a 1 M hydrochloric acid was added, and the resulting mixture was refluxed for 3 hours. A 3 M hydrochloric acid (6 mL) was added, and the reaction product was stirred for another 3 hours with heating, then cooled to 25°C, alkalinized with a 6 M aqueous solution of NaOH and extracted with dichloromethane (4 x 15 mL). The obtained crude product was purified by chromatography (SiO₂, PrOH/H₂O/NH₄OH = 8:1:1) to thereby afford 2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine (1.21 g, 86%).

[0197] Furthermore, optically active (S)- 2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine and (R)-2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine were synthesized by using the respective corresponding starting materials and reactants according to the above method.

[0198] (S)-2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine: 1 H NMR (CDCl₃, 400MHz) δ 1.40-1.80 (m, 5 H), 1.80-1.95 (m, 1 H), 2.12-2.21 (m, 1 H), 2.48-2.65 (m, 1 H), 2.66-2.78 (m, 2 H), 2.85-2.95 (m, 1 H), 3.26 (d, J = 13.2 Hz, 1 H), 3.93 (d, J = 13.2, 1 H), 7.20-7.40 (m, 4 H).

[0199] (R)-2-(Aminomethyl)-1-(4-chlorobenzyl)pyrrolidine exhibited the same ¹H NMR as that of the (S)-isomer.

[Example 913] Synthesis of 2-[[N(benzoylleucyl)aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 344)

[0200] EDCI (23 mg), HOBt (16.2 mg) and triethylamine (15.2 μ L) were added to a chloroform (1 mL) solution of 2-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine (22.5 mg, 0.10 mmol) and dl-benzoylleucine (0.12 mL), and the resulting mixture was stirred at 25 °C for 16 hours. The reaction mixture was diluted with dichloromethane (0.5 mL), washed with a 2 M aqueous solution of NaOH (0.75 mL \times 2), filtered through a PTFE membrane, thereby dried and concentrated to provide 2-[(N-benzoylleucyl)aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 344) (74 mg, quantitative). The purity was determined by RPLC/MS (85%). ESI/MS m/e 442 (M++H, $C_{23}H_{32}CIN_3O_2$).

[Examples 914 to 933]

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[0201] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 913. The obtained products, if necessary, were purified by chromatography (HPLC-C₁₈, acetonitrile/H₂O/TFA), and the objective compounds were obtained as TFA salts. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 19. Compd. Nos. 339 and 340 exhibited the following ¹H NMR, respectively.

Table 19

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Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)	
914	330	C ₂₁ H ₂₄ CIN ₃ O ₂	386	75*	Q	
915	331	C ₂₂ H ₂₆ Cl ₃ O ₂	400	44*	70	
916	332	C ₂₄ H ₃₀ CIN ₃ O ₅	476	57	Q	
917	333	C ₂₀ H ₂₃ CIN ₄ O ₂	387	40	Q	
918	334	C ₂₂ H ₂₆ CIN ₃ O ₂	400	68	Q	
919	335	C ₂₁ H ₂₃ CIN ₄ O ₄	431	73	Q	
920	336	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	454	75	Q	
921	337	C ₂₂ H ₂₆ CIN ₃ O ₂	400	68	Q	
922	338	C ₂₂ H ₂₆ CIN ₃ O ₂	400	70	Q	
923	341	C ₂₂ H ₂₆ CIN ₃ O ₂	400	80*	Q	
924	342	C ₂₂ H ₂₆ CIN ₃ O ₂	400	68	Q	
925	343	C ₂₄ H ₃₀ CIN ₃ O ₂	428	63	Q	
926	345	C ₂₃ H ₂₇ CIN ₂ O ₂	399	68*	Q	
927	346	C ₂₃ H ₂₆ CIFN ₂ O ₃	433	51	Q	
928	347	C ₂₄ H ₂₉ CIN ₂ O ₂	413	47	Q	
929	348	C ₂₃ H ₂₇ CIN ₂ O ₂	399	26	Q	
930	349	C ₂₁ H ₂₅ CIN ₂ O ₃ S	421	42	Q	
931	350	C ₂₆ H ₃₃ CIN ₂ O ₃	457	12.4	54	
932	351	C ₂₂ H ₂₆ CIN ₃ O ₃	416	34	81	
933	352	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₃	450	51	Q	
Notes: * indicates "yield (mg) of trifluoroacetate". Q means "Quantitative".						

[Example 934] Compd. No. 339: 82%; 1 H NMR (CDCl₃) 3 1.52-1.75 (m, 4 H), 1.84-1.95 (m, 1 H), 2.10-2.20 (m, 1 H), 2.67-2.78 (m, 1 H), 2.80-2.90 (m, 1 H), 3.10-3.20 (m, 1 H), 3.25 (d, J = 13.1 Hz, 1 H), 3.50-3.60 (m, 1 H), 3.89 (d, J = 13.1 Hz, 1 H), 4.28-4.20 (m, 2 H), 7.00-7.05 (m, 1 H), 7.12-7.29 (m, 4 H), 7.51 (t, J = 7.8 Hz, 1 H), 7.74 (d, J = 7.8 Hz, 1 H), 7.99 (d, J = 7.8 Hz, 1 H), 8.10-8.27 (m, 2 H).

[Example 935] Compd. No. 340: 68%; ^{1}H NMR (CDCl₃) δ 1.55-1.73 (m, 4 H), 1.86-1.97 (m, 1 H), 2.12-2.21 (m, 1 H), 2.67-2.76 (m, 1 H), 2.86-2.93 (m, 1 H), 3.14-3.21 (m, 1 H), 3.27 (d, J = 13.1 Hz, 1 H), 3.52-3.59 (m, 1 H), 3.89 (d, J = 13.1 Hz, 1 H), 4.09-4.21 (m, 2 H), 7.00-7.07 (m, 1 H), 7.12-7.30 (m, 4 H), 7.50 (t, J = 7.8 Hz, 1 H), 7.73 (d, J = 7.8 Hz, 1 H), 8.01 (d, J = 7.8 Hz, 1 H), 8.10-8.25 (m, 2 H).

[Reference Example 9] Synthesis of 3-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine

[0202] A 0.5 M dioxane solution of ammonia (60 mL, 30 mmol) was added to a mixture of 4-carboxy-1-(4-chlorobenzyl)pyrrolidin-2-one (5.05 g, 20 mmol) with EDCI (2.85 g, 22 mmol), HOBt (2.97 g, 22 mmol) and dichloromethane (100 mL). The resulting reaction mixture was stirred at room temperature for 15 hours and washed with 2 M HCI (three times) and a 2 M aqueous solution of NaOH (100 mL×4). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to thereby provide 4-carbamoyl-(4-chlorobenzyl)pyrrolidin-2-one (1.49 g) as a color-less solid.

[0203] A 1.0 M THF solution of BH₃ (25 mL) was added to a THF (15 mL) solution of 4-carbamoyl-1-(4-chlorobenzyl) pyrrolidin-2-one (1.49 g). The resulting reaction mixture was stirred for 15 hours and cooled to room temperature. The solvent was then removed under reduced pressure. Water (30 mL) and concentrated hydrochloric acid (10 mL) were added, and the mixture was stirred at 100 °C for 2 hours and at room temperature for 1 hour. A 2 M aqueous solution

of NaOH (100 mL) was added, and the obtained mixture was extracted with ethyl acetate (50 mL \times 3). The organic layers were combined, dried over K_2CO_3 , filtered, concentrated and purified by column chromatography (SiO₂, 15% methanol-5% triethylamine/dichloromethane) to thereby afford 3-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine (860 mg, 19%) as a colorless oil.

[Reference Example 10] Synthesis of 1-(4-chlorobenzyl)-3-[(glycylamino)methyl]pyrrolidine

[0204] A mixture of 3-(aminomethyl)-1-(4-chlorobenzyl)pyrrolidine (860 mg, 3.8 mmol) with triethylamine (5.7 mmol), N-tert-butoxycarbonylglycine (704 mg), EDCI (594 mg), HOBt (673 mg) and dichloromethane (20 mL) was stirred at room temperature for 15 hours, and dichloromethane (50 mL) was added to the mixture. The resulting solution was washed with a 2 M aqueous solution of NaOH (50 mL× 2), dried over anhydrous sodium sulfate, filtered and concentrated to thereby provide 3-[[N-(tert-butoxycarbonyl)glycl]aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (1.31 g, 90%). [0205] A 4 M dioxane solution of HCI (5 mL) was added to a methanol (10 mL) solution of 3-[[N-tert-butoxycarbonyl)glycyl]aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (804 mg, 2.11 mmol). The resulting solution was stirred at room temperature for 3.5 hours and then concentrated, and a 1 M aqueous solution of NaOH (20 mL) was added. The resulting mixture was extracted with dichloromethane (20 mL× 3), and the extracts were combined, dried over sodium sulfate and concentrated to thereby afford 1-(4-chlorobenzyl)-3-[(glycylamino)methyl]pyrrolidione (599 mg, 100%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 282.2 (M++H, C₁₄H₂₀CIN₃O).

[Example 936] Synthesis of 3-[[N-[3-trifluoromethylbenzoyl]glycyl]aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 1463)

[0206] A dichloromethane (0.2 mL) solution of 3-(trifluoromethyl)benzoyl chloride (0.058 mmol) was added to a mixture of a chloroform (0.2 mL) solution of 1-(4-chlorobenzyl)-3-[(glycylamino)methyl]pyrrolidine (0.050 mmol) with a dichloromethane (1 mL) solution of a piperidinomethylpolystyrene (60 mg). The resulting reaction mixture was stirred at room temperature for 2.5 hours, and methanol (0.30 mL) was then added. The reaction mixture was loaded onto a Varian™ SCX column and washed with methanol (15 mL). The obtained crude product was eluted with a methanol (5 mL) solution of 2 M NH₃ and concentrated to thereby provide 3-[[N-[3-trifluoromethylbenzoyl] glycyl]aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 1463) (22.4 mg, 99%). The purity was determined by RPLC/MS (97%). ESI/ MS m/e 454.2 (M++H, C₂₂H₂₃ClF₃N₃O₂).

[Examples 937 to 944]

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[0207] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 936. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 20.

Table 20

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
937	1464	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₃	470.0	21.0	89
938	1465	C ₂₃ H ₂₂ CIF ₆ N ₃ O ₂	522.0	24.5	94
939	1466	C ₂₁ H ₂₃ BrClN ₃ O ₂	466.0	20.8	90
940	1467	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	19.6	93
941	1468	C ₂₁ H ₂₃ CIN ₄ O ₄	431.2	19.5	91
942	1469	C ₂₂ H ₂₂ CIF ₄ N ₃ O ₂	472.0	21.8	92
943	1470	C ₂₁ H ₂₂ Cl ₃ N ₃ O ₂	456.0	22.1	97
944	1471	C ₂₁ H ₂₂ CIF ₂ N ₃ O ₂	422.0	20.9	99

[Example 945] Synthesis of 3-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 1506)

[0208] 2-Amino-4,5-difluorobenzoic acid (0.060 mmol), diisopropylcarbodiimide (0.060 mmol) and HOBt (0.060 mmol) were added to a solution of 1-(4-chlorobenzyl)-3-[(glycylamino)methyl]pyrrolidine (0.050 mmol) in chloroform (1.35 mL) and tert-butanol (0.05 mL). The resulting reaction mixture was stirred at room temperature for 19 hours, then

loaded onto a VarianTM SCX column and washed with methanol/chloroform = 1:1 (10 mL) and methanol (10 mL). The obtained crude product was eluted with a 2 M methanol solution of NH3 (5 mL) and concentrated to thereby afford 3-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 1506) (22.0 mg, quantitative). The purity was determined by RPLC/MS (92%). ESI/MS m/e 437 (M++H, C₂₁H₂₃CIF₂N₄O₂).

[Examples 946 to 952]

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[0209] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 945. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 21.

Table 21

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)			
946	1506	C _{21 24} BrClN ₄ O ₂	481	20.6	86			
947	1507	C ₂₁ H ₂₄ FCIN ₄ O ₂	419	21.7	Q			
948	1509	C ₂₇ H ₂₈ CIN ₃ O ₂	462	26.5	Q			
949	1510	C ₂₁ H ₂₄ CIIN ₄ O ₂	527	22.0	84			
950	1511	C ₁₉ H ₂₁ BrClN ₃ O ₂ S	472	23.7	Q			
951	1512	C ₂₁ H ₂₄ Cl ₂ N ₄ O ₂	435	22.3	Q			
952	1513	C ₂₇ H ₂₈ CIN ₃ O ₄ S	526	24.6	94			
Note:	Note: Q means "Quantitative".							

[Reference Example 11] Synthesis of 1-(4-chlorobenzyl)nipecotic acid

[0210] 4-Chlorobenzyl chloride (6.42 g, 39.9 mmol) and ⁱPr₂NEt (7.74 g, 40.0 mmol) were added to an acetonitrile (15 mL) solution of ethyl nipecotate (6.29 g, 40.0 mmol). The resulting reaction mixture was stirred at 70 °C for 1.5 hours, and the solvent was removed under reduced pressure. A saturated aqueous solution of NaHCO₃ (50 mL) was added to the residue, and the resulting mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with a saturated aqueous solution of NaHCO₃ and dried over Na₂SO₄. The solvent was removed under reduced pressure to thereby provide ethyl 1-(4-chlorobenzyl)nipecotate as a reddish yellow oil. (11.0 g, 97.8%). The resulting oil was used without purification. The purity was determined by RPLC/MS (97%). ESI/MS m/e 382.2 (M*+H, C₁₅H₂₁CINO₂).

[0211] An H₂O (25 mL) solution of LiOH (1.66 g) was added to a THF (60 mL) solution of ethyl 1-(4-chlorobenzyl) nipecotate. The resulting reaction mixture was stirred at room temperature for 1.5 hours. The solvent was removed under reduced pressure to provide an amorphous solid. The obtained crude product was purified by column chromatography (SiO₂, 50% methanol-dichloromethane) to afford 1-(4-chlorobenzyl)nipecotic acid (9.75 g, 98.2%) as an off-while amorphous solid. The purity was determined by RPLC/MS (>95%). ESI/MS m/e 254.0 (M++H, C₁₃H₁₇CINO₂).

[Reference Example 12] Synthesis of 1-(4-chlorobenzyl-3-[(tert-butoxycarbonyl)amino]piperidine

[0212] Triethylamine (3.38 g) and activated 3 Å molecular sieve (30 g) were added to a ^tBuOH (500 mL) solution of 1-(4-chlorobenzyl)nipecotic acid (7.06 g, 27.8 minol). Diphenylphosphoryl azide (8.58 g) was added, and the resulting reaction mixture was stirred under reflux for 18 hour and cooled. The solvent was removed under reduced pressure. The obtained residue was then dissolved in ethyl acetate (500 mL), and the organic layer was washed with a saturated aqueous solution of NaHCO₃ (100 mL×2) and brine (50 mL), then dried (over Na₂SO₄) and concentrated under reduced pressure. The obtained crude product was purified by chromatography (SiO₂, 25% ethyl acetate-hexane) to provide 1-(4-chlorobenzyl-3-[(tert-butoxycarbonyl)amino]piperidine (2.95 g, 32.6%) as a white crystalline solid. ¹H NMR (CDCl₃, 300MHz) δ 1.4-1.75 (br, 4 H), 2.2-2.7 (br, 4 H), 3.5 (br, 2 H), 3.8 (br, 4 H), 7.3 (br, 4 H). The purity was determined by RPLC/MS (>99%). ESI/MS m/e 269.2 (M*+H-56, C₁₇H₂₆CIN₂O₂).

[Reference Example 13] Synthesis of 3-amino-1-(4-chlorobenzyl)piperidine

[0213] To a methanol (25 mL) solution of 1-(4-chlorobenzyl)-3-[(tert-butoxycarbonyl)amino]piperidine (2.55 g, 7.85 mmol), was added 1M HCl-Et₂O (50 mL). The resulting reaction mixture was stirred at 25 °C for 15 hours, and the

solvent was removed under reduced pressure to afford 3-amino 1-(4-chlorobenzyl)piperidine dihydrochloride as an amorphous solid (2.49 g, quantitative). The purity was determined by RPLC/MS (>95%). ESI/MS m/e 225.2 (M $^+$ +H, C $_{12}H_{18}CIN_2$).

[Example 953] Synthesis of 1-(4-chlorobenzyl)-3-[[N-(3-methylbenzoyl)glycyl]amino]piperidine (Compd. No. 355)

[0214] N-(3-Methylbenzoyl)glycine (10.6 mg, 0.055 mmol), EDCI (10.5 mg) and 1-hydroxybenzotriazole hydrate (7.4 g) were added to a chloroform (2.5 mL) solution of 1-(4-chlorobenzyl)-3-aminopiperidine dihydrochloride (1.49 mg, 0.050 mmol) and triethylamine (15.2 mg). The resulting reaction mixture was stirred at 25 °C for 16 hours and washed with a 2 N aqueous solution of NaOH (2 mL \times 2) and brine (1 mL). After filtration through a PTFE membrane, the solvent was removed under reduced pressure to provide 1-(4-chlorobenzyl)-3-[[N-(3-methylbenzoyl)glycyl]amino]piperidine (Compd. No. 355) (17.4 mg, 87%). The purity was determined by RPLC/MS (97%). ESI/MS m/e 400.0 (M++H, $C_{22}H_{26}CIN_3O_2$).

Examples 954 to 982]

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[0215] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 953. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 22. The Compd. No. 358 exhibited the following ¹H NMR.

Table 22

Example	Compd. No	Molecular Formula	ESI/MS m/e	Yield (mg)	Yeld (%)
954	354	C ₂₁ H ₂₄ ClN ₃ O ₂	386	16.1	83
955	356	C ₂₀ H ₂₃ CIN ₄ O ₂	387	19.4	100
956	357	C ₂₂ H ₂₆ CIN ₃ O ₂	400	16.8	84
957	359	C ₂₂ H ₂₆ CIN ₃ O ₂	400	8.9	17
958	360	C ₂₂ H ₂₅ CIN ₄ O ₄	445	25.6	Q
959	361	C ₂₃ H ₂₇ CIN ₂ O ₂	399	15.5	29
960	362	C ₂₄ H ₂₉ ClN ₂ O ₃	429	12.4	58
961	363	C ₂₁ H ₂₅ CIN ₂ O ₂ S	405	22.2	Q
962	364	C ₂₄ H ₂₉ CIN ₂ O ₄	445	20.7	93
963	365	C ₂₄ H ₂₉ ClN ₂ O ₂	413	15.6	75
964	366	C ₂₃ H ₂₆ CIFN ₂ O ₃	433	21.6	100
965	367	$C_{23}H_{27}CIN_2O_2$	399	11.9	60
966	368	C ₂₂ H ₂₅ CIN ₂ O ₂	385	16.0	83
967	369	C ₂₂ H ₂₄ Cl ₂ N ₂ O ₂	419	13.9	60
968	370	C ₂₆ H ₃₃ CIN ₂ O ₃	457	∙15.9	54
969	371	C ₂₅ H ₃₁ CIN ₂ O ₃	443	19.6	84
970	372	C ₂₁ H ₂₅ CIN ₂ O ₃ S	421	23.0	Q
971	373	$C_{23}H_{28}CIN_3O_2$	414	19.1	92
972	374	C ₂₄ H ₃₀ CIN ₃ O ₃	444	18.6	84
973	375	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂	448	18.0	80
974	376	C ₂₄ H ₃₀ CIN ₃ O ₃	444	19.6	88
975	377	C ₂₅ H ₃₁ Cl ₂ N ₃ O ₂	476	20.7	87 .
976	378	C ₂₇ H ₃₃ CIFN ₃ O ₂	486	23.9	98
977	379	$C_{25}H_{30}CIN_3O_3$	456	33.3	Q

Table 22 (continued)

Example	Compd. No	Molecular Formula	ESI/MS m/e	Yield (mg)	Yeld (%)		
978	380	C ₂₄ H ₃₀ CIN ₃ O ₂	428	9.8	46		
979	381	C ₂₁ H ₂₆ CIN ₃ O ₃ S	436	10.3	47		
980	382	C ₂₂ H ₂₆ CIN ₃ O ₃	416	24.4	Q		
981	383	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₃	450	27.5	Q		
Note:	Note: Q means "Quantitative".						

[Example 982] Compd. No. 358: 88%; 1 H NMR (CDCl₃) 3 1.53-1.75 (m, 4 H), 2.12-2.20 (m, 1 H), 2.37-2.50 (m, 2 H), 2.53-2.61 (m, 1 H), 3.38-3.50 (m, 2 H), 2.53-2.61 (m, 1 H), 3.38-3.50 (m, 2 H), 4.06-4.20 (m, 3 H), 7.10-7.13 (m, 1 H), 7.18-7.30 (m, 4 H), 7.59 (t, J = 7.8 Hz, 1 H), 7.79 (d, J = 7.8 Hz, 1 H), 8.01 (d, J = 7.8 Hz, 1 H), 8.11(s, 1 H).

[Reference Example 14] Synthesis of 1-benzyl-4-[[N-(tert-butoxycarbonyl)glycyl]amino]piperidine

[0216] N-(tert-Butoxycarbonyl)glycine (3.48 g, 20 mmol), EDCI (4.02 g, 21 mmol) and HOBt (2.83 g, 21 mmol) were added to a dichloromethane (40 mL) solution of 4- amino-1-benzylpiperidine (3.80 g, 20 mmol). The resulting reaction mixture was stirred at room temperature for 12 hours, and a 2 M solution of NaOH was then added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (20 mL×2). The organic layers were combined, washed with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography (SiO₂, ethyl acetate/methanol/triethylamine = 85: 12:3) to afford 1-benzyl-4-[[N-(tert-butoxycarbonyl)glycyl]amino]piperidine (6.59 g, 95%).

[Reference Example 15] Synthesis of 1- benzyl-4-(glycylamino)piperidine

[0217] A 4 M dioxane solution of HCI was added to a methanol (80 mL) solution of 1- benzyl-4-[N-(tert-butoxycarbonyl) glycyl]aminopiperidine (6.59 g). The resulting solution was stirred at room temperature for 2 hours and concentrated. A 2 M aqueous solution of NaOH (20 mL) was then added to the solution. The resulting mixture was extracted with dichloromethane (40 mL). The extracts were combined, dried over anhydrous sodium sulfate and concentrated. The obtained crude product was purified by column chromatography (SiO₂, ethyl acetate/methanol/triethylamine = 85:12: 3) to thereby provide 1-benzyl-4-(glycylamino)piperidine (3.91 g, 83%). 1 H NMR (CDCl₃, 400 MHz) δ 1.47-1.59 (m, 2 H), 1.59 (br, 2 H), 1.76-1.96 (m, 2 H), 2.10-2.19 (m, 2 H), 2.75-2.87 (m, 2 H), 3.29 (s, 2 H), 3.50 (s, 2 H), 3.65-3.89 (m, 1 H), 7.15-7.23 (m, 1 H), 7.23-7.33 (m, 5 H).

[0218] Other 4-acylamino-1-benzylpiperidines were synthesized by using the respective corresponding starting materials and reactants according to the methods of Reference Examples14 and 15.

[0219] 4-(β-alanylamino)-1-benzylpiperidine: 2.46 g, 51% (two steps)

[0220] 1-benzyl-4-((S)-leucylamino)piperidine: 1.78 g, 74% (two steps) and 1-benzy-4-((R)-leucylamine)piperidine: 1.48 g, 61% (two steps).

[Example 983] Synthesis of 4-(N-benzoylglycyl)amino-1-benzylpiperidine (Compd. No. 386)

[0221] A chloroform (0.4 mL) solution of benzoyl chloride (0.060 mmol) was added to a chloroform (1.0 mL) solution of 1-benzyl-4-(glycylamino)piperidine (0.050 mmol) and triethylamine (0.070 mmol). The resulting reaction mixture was shaken at room temperature for 12 hours, and an (aminomethyl)polystyrene resin (1.04 mmol/g, 50 mg, 50 mmol) was added to the mixture. The obtained mixture was shaken at room temperature for 12 hours. The resulting reaction mixture was filtered, and the resin was washed with dichloromethane (0.5 mL). The filtrate and washings were combined, and dichloromethane (4 mL) was added. The solution was washed with a 2 M aqueous solution of NaOH (0.5 mL) to provide 4-(N-benzoylglycyl)amino-1-benzylpiperidine (Compd. No. 386) (11.3 mg, 64%). The purity was determined by RPLC/MS (94%). ESI/MS m/e 352.0 (M*+H, C₂₁H₂₅N₃O₂).

[Examples 984 to 1034]

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[0222] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 983. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 23.

Table 23

Example	Compd. No	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
984	384	C ₂₂ H ₂₆ CIN ₃ O ₂	400	60.0	Q
985	385	C ₂₁ H ₂₃ CIN ₄ O ₄	431	58.7	91
986	. 387	$C_{25}H_{27}N_3O_2$	402.5	15.5	77
987	388	C ₂₁ H ₂₄ N ₄ O ₄	397.0	16.2	82
988	389	C ₂₃ H ₂₇ N ₃ O ₄	410.0	16.2	79
989	390	$C_{22}H_{24}F_3N_3O_2$	420.0	17.4	83
990	391	C ₂₂ H ₂₃ F ₄ N ₃ O ₂	438.0	18.4	84
991	392	$C_{22}H_{24}F_3N_3O_3$	436.0	17.1	79
992	393	C ₂₁ H ₂₄ BrN ₃ O ₂	430.0	18.0	84
993	394	C ₂₁ H ₂₄ CIN ₃ O ₂	386.0	16.4	85
994	395	C ₂₁ H ₂₄ BrN ₃ O ₂	430.0	17.2	80
995	396	$C_{21}H_{23}F_2N_3O_2$	388.0	15.1	78
996	397	C ₂₁ H ₂₃ Cl ₂ N ₃ O ₂	420.0	11.7	56
997	398	C ₂₂ H ₂₇ N ₃ O ₂	366.0	13.1	72
998	399	C ₂₆ H ₂₉ N ₃ O ₂	416.0	15.8	76
999	400	C ₂₂ H ₂₆ N ₄ O ₄	411.0	17.4	85
1000	401	C ₂₄ H ₂₉ N ₃ O ₄	424.0	16.9	80
1001	402	C ₂₃ H ₂₆ F ₃ N ₃ O ₂	434.0	17.7	82
1002	403	C ₂₃ H ₂₅ F ₄ N ₃ O ₂	452.0	18.6	82
1003	404	C ₂₃ H ₂₆ F ₃ N ₃ O ₃	450.0	17.8	79
1004	405	C ₂₂ H ₂₆ BrN ₃ O ₂	444.0	17.9	81
1005	406	C ₂₂ H ₂₆ CIN ₃ O ₂	400.0	15.5	78
1006	407	C ₂₂ H ₂₆ BrN ₃ O ₂	444.0	17.8	80
1007	408	C ₂₂ H ₂₅ F ₂ N ₃ O ₂	402.0	15.6	78
1008	409	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₂	434.0	17.6	81
1009	410	C ₂₅ H ₃₃ N ₃ O ₂	408.0	16.2	79
1010	411	$C_{29}H_{35}N_3O_2$	458.5	18.8	82
1011	412	C ₂₅ H ₃₂ N ₄ O ₄	453.0	19.4	86
1012	413	$C_{27}H_{35}N_3O_4$	466.0	19.8	85
1013	414	$C_{26}H_{32}F_3N_3O_2$	476.0	20.2	85
1014	415	C ₂₆ H ₃₁ F ₄ N ₃ O ₂	494.0	20.5	83
1015	416	C ₂₆ H ₃₂ F ₃ N ₃ O ₃	492.0	19.5	79
1016	417	C ₂₅ H ₃₂ BrN ₃ O ₂	486.0	19.1	79
1017	418	C ₂₅ H ₃₂ CIN ₃ O ₂	442.0	17.7	80
1018	419	C ₂₅ H ₃₂ BrN ₃ O ₂	486.0	20.3	83
1019	420	C ₂₅ H ₃₁ F ₂ N ₃ O ₂	444.0	18.6	84
1020	421	C ₂₅ H ₃₁ Cl ₂ N ₃ O ₂	476.0	19.4	81

Table 23 (continued)

Example	Compd. No	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)		
1021	422	$C_{25}H_{33}N_3O_2$	408.0	14.4	71		
1022	423	C ₂₉ H ₃₅ N ₃ O ₂	458.0	16.4	72		
1023	424	C ₂₅ H ₃₂ N ₄ O ₄	453.0	18.1	80		
1024	425	C ₂₇ H ₃₅ N ₃ O ₄	466.0	16.4	70		
1025	426	C ₂₆ H ₃₂ F ₃ N ₃ O ₂	476.0	17.3	73		
1026	427	C ₂₆ H ₃₁ F ₄ N ₃ O ₂	494.0	18.8	76		
1027	428	C ₂₆ H ₃₂ F ₃ N ₃ O ₃	492.0	18.4	75		
1028	429	C ₂₅ H ₃₂ BrN ₃ O ₂	486.0	17.9	74		
1029	430	C ₂₅ H ₃₂ CIN ₃ O ₂	442.0	15.7	71		
1030	431	C ₂₅ H ₃₂ BrN ₃ O ₂	486.0	17.7	73		
1031	432	C ₂₅ H ₃₁ F ₂ N ₃ O ₂	444.0	16.6	75		
1032	433	C ₂₅ H ₃₁ Cl ₂ N ₃ O ₂	476.0	18.7	78		
1033	1016	C ₂₂ H ₂₃ CIF ₃ N ₃ O ₂	454	32.5*	53		
1034	1017	C ₂₁ H ₂₄ CIN ₃ O ₂	386	55.2*	Q		
	Notes: * indicates "yield (mg) of trifluoroacetate". Q means "Quantitative".						

[Reference Example 16] Synthesis of 3-carbamoyl-1-(4-chlorobenzyl)piperidine

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[0223] Triethylamine (7.0 mL, 50 mmol) and 4-chlorobenzyl chloride (8.05 g, 50 mmol) were added to a solution of nipecotamide (6.40 g, 50 mmol) in acetonitrile (150 mL) and ethanol (20 mL). The resulting reaction mixture was stirred at 50 °C for 16 hours and cooled to room temperature. A saturated aqueous solution of NaHCO₃ (50 mL) and water (150 mL) were then added, and the resulting mixture was extracted with ethyl acetate (150 mL×3). The extracts were washed with brine, dried over Na₂SO₄ and concentrated to afford a light-red solid. The obtained crude solid was washed with ether (100 mL) to provide 3-carbamoyl-1-(4-chlorobenzyl)piperidine (6.98 g, 54%).

[Reference Example 17] Synthesis of 3-(aminomethyl)-1-(4-chlorobenzyl)piperidine

[0224] 3-Carbamoyl-1-(4-chlorobenzyl)piperidine (3.80 g, 15 mmol) was dissolved in THF (30 mL), and 1 M BH₃-THF (9.4 mL) was added to the obtained solution. The resulting mixture was stirred at 70 °C for 15 hours. After cooling to 0 °C, a 2 M hydrochloric acid (50 mL) was added, and the mixture was stirred at room temperature for another 3 hours, basicified with an 4 M aqueous solution of NaOH and extracted with ethyl acetate (100 mL×3). The extracts were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The obtained crude product was purified by column chromatography (SiO₂, ethyl acetate/ethanol/triethylamine = 80:15:5) to thereby provide 3-(aminomethyl)-1-(4-chlorobenzyl)piperidine (2.05 g, 55%). ¹H NMR (CDCl₃, 400MHz) δ 1.00-1.09 (m, 1 H), 1.50-1.87 (m, 7 H), 1.97-2.06 (m, 1 H), 2.65-2.77 (m, 2 H), 3.16-3.26 (m, 2 H), 3.32 (s, 2 H), 3.40 (d, J = 13.3 Hz, 1 H), 3.49 (d, J = 13.3 Hz, 1 H), 7.22-7.33 (m, 5 H).

[Example 1035] Synthesis of 3-[(N-benzoylglycyl)amino]methyl-1-(4-chlorobenzyl)piperidine (Compd. No. 434)

[0225] A chloroform (0.4 mL) solution of benzoyl chloride (0.060 mmol) was added to a chloroform (1.0 mL) solution of 3-[(glycylamino)methyl-1-(4-chlorobenzyl)piperidine (0.050 mmol) and triethylamine (0.070 mmol). The resulting reaction mixture was shaken at room temperature for 2.5 hours, and an (aminomethyl)polystyrene resin (1.04 mmol/g, 50 mg, 50 mmol) was then added to the obtained mixture. The resulting mixture was shaken at room temperature for 12 hours and filtered, and the resin was washed with dichloromethane (0.5 mL). The filtrate and washings were combined, and dichloromethane (4 mL) was added. The obtained mixture was washed with an 2 M aqueous solution of NaOH (0.5 mL) and concentrated to thereby afford 3-[(N-benzoylglycyl)amino]methyl-1-(4-chlorobenzyl)piperidine (Compd. No. 434) (14.7 mg, 74%). The purity was determined by RPLC/MS (91%). ESI/MS m/e 400 (M++H,

 $C_{22}H_{26}CIN_3O_2$).

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[Examples 1036 to 1058]

⁵ [0226] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1035. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 24.

Table 24

panters	Table 24						
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)		
1036	435	C ₂₆ H ₂₈ CIN ₃ O ₂	450	16.0	71		
1037	436	C ₂₂ H ₂₅ CIN ₄ O ₄	445	18.9	85		
1038	437	C ₂₄ H ₂₈ CIN ₃ O ₄	458	18.2	79		
1039	438	C ₂₃ H ₂₅ CIF ₃ N ₃ O ₂	468	19.0	81		
1040	439	C ₂₃ H ₂₄ CIF ₄ N ₃ O ₂	486	20.2	83		
1041	440	C ₂₃ H ₂₅ CIF ₃ N ₃ O ₃	484	18.9	78		
1042	441	C ₂₂ H ₂₅ BrClN ₃ O ₂	478	19.2	80		
1043	442	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₂	434	17.3	80		
1044	443	C ₂₂ H ₂₅ BrClN ₃ O ₂	478	18.8	79		
1045	444	C ₂₂ H ₂₄ CIF ₂ N ₃ O ₂	436	16.7	77		
1046	445	C ₂₂ H ₂₄ Cl ₃ N ₃ O ₂	468	17.9	76		
1047	446	C ₂₃ H ₂₈ CIN ₃ O ₂	414	14.6	71		
1048	447	C ₂₇ H ₃₀ CIN ₃ O ₂	464	17.0	73		
1049	448	C ₂₃ H ₂₇ CIN ₄ O ₄	459	19.5	85		
1050	449	C ₂₅ H ₃₀ ClN ₃ O ₄	472	17.1	72		
1051	450	C ₂₄ H ₂₇ CIF ₃ N ₃ O ₂	482	19.4	81		
1052	451	C ₂₄ H ₂₆ CIF ₄ N ₃ O ₂	500	18.2	73		
1053	452	C ₂₄ H ₂₇ CIF ₃ N ₃ O ₃	498	18.8	76		
1054	453	C ₂₃ H ₂₇ BrClN ₃ O ₂	492	19.4	79		
1055	454	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂	448	16.5	. 74		
1056	455	C ₂₃ H ₂₇ BrClN ₃ O ₂	492	19.3	78		
1057	456	C ₂₃ H ₂₆ CIF ₂ N ₃ O ₂	450	17.1	76		
1058	457	C ₂₃ H ₂₆ Cl ₃ N ₃ O ₂	482	16.9	70		

[Reference Example 18] Synthesis of 4-(aminomethyl)-1-(4-chlorobenzyl)piperidine

[0227] K_2CO_3 (3.02 g) and 4-chlorobenzyl chloride (3.52 g, 21.8 mmol) were successively added to an acetonitrile (100 mL) solution of 4-(aminomethyl)piperidine (7.00 g, 61.3 mmol). The resulting reaction mixture was stirred at 60 °C for 16 hours, cooled to 25 °C and concentrated. The obtained residue was fractionated between dichloromethane (75 mL) and water (50 mL) and then washed with water (50 mL×2) and brine (50 mL×1). The organic layer was dried (over MgSO₄), concentrated and then purified by chromatography (SiO₂, 4% H₂O-ⁱPrOH) to provide 4-(aminomethyl)-1-(4-chlorobenzyl)piperidine (3.58 g, 69%).

[Example 1059] Synthesis of 4-[(N-benzoylglycyl)amino]methyl-1-(4-chlorobenzyl)piperidine (Compd. No. 458)

[0228] Hippuric acid (38 mg, 0.21 mmol), EDCI (48 mg, 0.24 mmol), HOBt (31 mg, 0.23 mmol) and triethylamine (38 μ L, 0.27 mmol) were added to a dichloromethane (1 mL) solution of 4-(aminomethyl)-1-(4-chlorobenzyl)piperidine (50

mg, 0.21 mmol). The resulting reaction mixture was shaken at 25 °C for 16 hours, then diluted with 1 mL of dichloromethane, washed with a 2 M aqueous solution of NaOH (0.75 mL \times 2), dried (over MgSO₄), concentrated and purified by chromatography (SiO₂, 6-8% methanol/dichloromethane) to thereby afford 4-[(N-benzoylglycyl)amino]methyl-1-(4-chlorobenzyl)piperidine (Compd. No. 458). The resulting compound was treated with TFA to provide a TFA salt (105 mg, 97%). The purity was determined by RPLC/MS (85%). ESI/MS m/e 400 (M*+H, $C_{22}H_{26}CIN_3O_2$).

[Examples 1060 to 1086]

[0229] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1059. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 25.

Table 25

Table 23							
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)		
1060	459	C ₂₃ H ₂₈ CIN ₃ O ₂	414	86*	78		
1061	460	C ₂₃ H ₂₈ CIN ₃ O ₂	414	55	Q		
1062	461	C ₂₃ H ₂₅ CIF ₃ N ₃ O ₂	468	65	Q		
1063	462	C ₂₃ H ₂₈ CIN ₃ O ₂	414	61	Q		
1064	463	C ₂₃ H ₂₈ CIN ₃ O ₂	414	54	Q		
1065	464	C ₂₅ H ₃₂ CIN ₃ O ₅	490	56	Q		
1066	465	C ₂₁ H ₂₅ CIN ₄ O ₂	401	38	96		
1067	466	C ₂₂ H ₂₅ CIN ₄ O ₄	445	15	34		
1068	557	C ₂₃ H ₂₈ CIN ₃ O ₂	414	58*	66		
1069	558	C ₂₃ H ₂₈ CIN ₃ O ₂	414	55	Q		
1070	618	C ₂₅ H ₃₂ CIN ₃ O ₂	442	58	Q		
1071	686	C ₂₆ H ₃₄ CIN ₃ O ₂	456	62	Q		
1072	749	C ₃₄ H ₃₇ CIN ₄ O ₂	569	7.2*	18		
1073	750	C ₂₄ H ₃₀ CIN ₃ O ₃	444	4.7*	14		
1074	840	C ₂₄ H ₂₉ CIN ₂ O ₂	413	52*	58		
1075	841	C ₂₃ H ₂₇ CIN ₂ O ₂	399	52	Q		
1076	842	C ₂₃ H ₂₆ Cl ₂ N ₂ O ₂	433	55	Q		
1077	843	C ₂₅ H ₃₁ ClN ₂ O ₂	427	58	Q		
1078	844	C ₂₄ H ₂₉ CIN ₂ O ₂	413	56	Q		
1079	845	C ₂₄ H ₂₉ CIN ₂ O ₄ S	477	62	Q		
1080	846	C ₂₉ H ₃₁ CIN ₂ O ₃	491	43	88		
1081	847	C ₂₄ H ₂₈ CIFN ₂ O ₃	447	54	Q		
1082	848	C ₂₅ H ₃₁ CIN ₂ O ₂	427	47	Q		
1083	849	C ₂₅ H ₃₁ ClN ₂ O ₄	459	55	Q		
1084	850	C ₂₂ H ₂₇ CIN ₂ O ₃ S	435	46	Q		
1085	873	C ₂₀ H ₂₈ CIN ₃ O ₂	378	44.8	Q		
1086	874	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₃	464	51	Q		
	* indicates "yie ins "Quantitativ	eld (mg) of trifluoroace e".	tate".				

[Reference Example 19] Synthesis of 1-(4-chlorobenzyl)-4-[N-(3,3-diphenylpropyl)aminomethyl]piperidine

[0230] 4-(Aminomethyl)-1-(4-chlorobenzyl)piperidine (120 mg) was reacted with 3,3-diphenylpropyl methanesulfonate (1.0 equivalent) in the presence of NaI (2.6 equivalents) in acetonitrile at 70 °C for 16 hours. After treatment by a conventional method, the obtained crude product was purified by column chromatography (SiO₂) to afford 1-(4-chlorobenzyl)-4-[N-(3,3-diphenylpropyl)aminomethyl]piperidine (118 mg, 54%). The purity was determined by RPLC/MS (98%).

[Reference Example 20] Synthesis of 1-(4-chlorobenzyl)-4-[N-(2,2-diphenylethyl)aminomethyl]piperidine

[0231] 4-(Aminomethyl)-1-(4-chlorobenzyl)piperidine (120 mg) was subjected to reducing amination in methanol by using 2,2-diphenylacetaldehyde (0.66 equivalent) and a polymer-supported boron hydride at 25 °C for 16 hours and then subjected to treatment according to a conventional method and column chromatography (SiO₂) to thereby provide 1-(4-chlorobenzyl)-4-[N-(2,2-diphenylethyl)aminomethyl]piperidine (70 mg, 49%). The purity was determined by RPLC/MS (98%).

[Example 1087] Synthesis of 4- [N-(N-benzoylglycyl)-N-(2,2-diphenylethyl)aminomethyl]-1-(4-chlorobenzyl)piperidine (Compd. No. 524)

[0232] Hippuric acid (1.1 equivalents), HBTU (1.1 equivalents) and HOBt (1.1 equivalents) were added to a dichloromethane solution of 1-(4-chlorobenzyl)-4-[N-(2,2-diphenylethyl)aminomethyl]piperidine (0.084 mmol). The resulting reaction mixture was stirred at 40 °C for 24 hours. The obtained crude product was subjected to treatment according to a conventional method and preparative TLC (SiO₂) to thereby provide 4-[N-(N-benzoylglycyl)-N-(2,2-diphenylethyl) aminomethyl]-1-(4-chlorobenzyl)piperidine (Compd. No. 524) (8.5 mg, 17%). The purity was determined by RPLC/MS (98%). ESI/MS m/e 580 (M*+H, C₃₆H₃₈ClN₃O₂).

[Examples 1088 to 1090]

[0233] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1087. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 26.

		Table Le			
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield(mg)	Yield (%)
1088	521	C ₃₈ H ₃₉ CIF ₃ N ₃ O ₂	662	5.5	10
1089	522	C ₃₇ H ₃₇ CIF ₃ N ₃ O ₂	648	8.6	16
1090	523	C ₃₇ H ₄₀ CIN ₃ O ₂	594	4.8	10

Table 26

[Reference Example 21] Synthesis of 1-(4-chlorobenzyl)-4-[(valylamino)methyl]piperidine

[0234] Triethylamine (0.76 mL, 5.44 mmol), di-N-(tert-butoxycarbonyl)valine (1.09 g, 5.03 mmol), EDCI (883 mg, 4.61 mmol) and HOBt (623 mg, 4.61 mmol) were added to a dichloromethane (21 mL) solution of 4-(aminomethyl)-1-(4-chlorobenzyl)piperidine (1.0 g, 4.2 mmol). The resulting reaction mixture was stirred at 25 °C for 16 hours, then diluted with dichloromethane (20 mL), washed with a 2 M aqueous solution of NaOH (20 mL \times 2) and brine (20 mL \times 1), dried (over MgSO₄) and concentrated, The obtained crude product was purified by chromatography (SiO₂, 3% methanol/dichloromethane) to thereby afford 1-(4-chlorobenzyl)-4-[[(N-Boc-valyl)amino]methyl]piperidine (1.1 g, 60%) as a light amber oil. ESI/MS m/e 438 (M++H).

[0235] 1-(4-Chlorobenzyl)-4-[[(N-Boc-valyl)amino]methyl]piperidine (1.1 g, 2.51 mmol) was dissolved in a 3 M HCI-methanol solution (25 mL) and stirred at 25 °C for 1 hour. The resulting reaction mixture was concentrated, and the obtained salt was dissolved in ^tBuOH/H₂O =3:1 (25 mL). An anion (OH⁻) exchange resin was added until the solution became slightly basic. The obtained mixture was filtered and concentrated to provide 1-(4-chlorobenzyl)-4-[(valylamino) methyl]piperidine (819 mg, 97%). Further purification was not required for the resulting compound. ESI/MS m/e 338.1 (M⁺+H, C₁₈H₂₈CIN₃O).

[0236] Other 4-[(acylamino)methyl]-1-(4-chlorobenzyl)piperidines were synthesized by using the respective corresponding starting materials and reactants according to the method of Reference Example 21.

[0237] 1-(4-chlorobenzyl)-4-[(glycylamino)methyl]piperidine: 0.830g, 67% (two steps), ESI/MS 269 (M++H).

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- [0238] 1-(4-chlorobenzyl)-4-[(serylamino)methyl]piperidine: 0.286 g, 20% (two steps), ESI/MS 326 (M++H).
- [0239] 4-[(alanylamino)methyl]-1-(4-chlorobenzyl)piperidine: 1.20g, 65% (two steps), ESI/MS 310 (M++H).
- [0240] 1-(4-chlorobenzyl)-4-[(prolylamino)methyl]piperidine:1.48g, 86% (two steps), ESI/MS 336 (M++H).
- [0241] 1-(4- chlorobenzyl)-4 -[(glutaminylamino)methyl]piperidine: 0.830g, 27% (two steps), ESI/MS 367 (M++H).
- [0242] 1-(4-chlorobenzyl)-4-[((2-methylalanyl)amino)methyl]piperidine: 2.24 g, 62% (two steps), ESI/MS 324 (M++H).
 - [0243] 1-(4-chlorobenzyl)-4 -[((O-methylseryl)amino)methyl]piperidine: 0.686 g, 38% (two steps), ESI/MS 340 (M^++H) .
- [0244] 1-4-chlorobenzyl)-4-[((1-aminocyclopropylcarbonyl)amino)methyl]piperidine: 2.03g, 82% (two steps), ESI/ MS 322 (M++H).
- [0245] 1-(4-chlorobenzyi)-4-[(leucylamino)methyl]piperidine: 1.30 g, 58% (two steps), ESI/MS 352 (M++H).
- [0246] 1-(4-chlorobenzyl)-4-[((O-benzylseryl)amino)methyl]piperidine: 1.34 g, 56% (two steps), ESI/MS 416 (M++H).

[Reference Example 22] <u>Synthesis of 1-(tert-butoxycarbonyl)-4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]</u> aminomethyl]piperidine

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[0247] Triethylamine (3.51 g), N-(9-fluorenylmethyloxycarbonyl)glycine (7.93 g, 26.7 mmol), EDCI (3.80 g) and HOBt (4.33 g) were added to a dichloromethane (150 mL) solution of 4-(aminomethyl)-1-(tert-butoxycarbonyl)piperidine (5.72 g). The resulting reaction mixture was stirred at room temperature for 18 hours, then washed with water (100 mL \times 3) and brine (100 mL \times 2), dried over anhydrous sodium sulfate, concentrated and recrystallized from acetonitrile/methanol (150 mL/1 mL) at 0 °C to provide 1-(tert-butoxycarbonyl)-4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine (5.75 g, 44%) as an off-white crystal.

[Reference Example 23] Synthesis of 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine

[0248] 1-(tert-Butoxycarbonyl)-4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine (3.17 g, 6.42 mmol) was added to a 4 M dioxane solution of HCl. The resulting solution was stirred at room temperature for 5 hours and concentrated to afford 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine (3.85 g) as an off-white solid. The obtained product was used without further purification.

 $[Reference\ Example\ 24]\ \underline{Synthesis\ of\ 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]-1-(4-methylthiobenzyl)}\\ piperidine$

[0249] 4-Methylthiobenzaldehyde (1.24 g) and NaBH(OAc)₃ (2.56 g) were added to a 1% acetic acid/DMF (15 mL) solution of 4-[[N-(9-fluorenylmethyloxycarbony)glycyl]aminomethyl]piperidine (1.00 g, 2.33 mmol). The resulting reaction mixture was stirred at 60 °C for 1 hour, cooled to room temperature and concentrated. A saturated aqueous solution (50 mL) of NaHCO₃ was added to the resultant residue, and the obtained mixture was extracted with ethyl acetate (50 mL× 2). The extracts were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude product was purified by column chromatography (SiO₂, 50%-10% methanol-dichloromethane) to thereby afford 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]-1-(4-methylthiobenzyl)piperidine (602 mg) as a colorless oil.

[Reference Example 25] Synthesis of 1-(4-ethylbenzyl)-4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl] piperidine

45 [0250] 4-Ethylbenzaldehyde (1.09 g, 8.16 mmol) and NaBH₃CN (6.59 g, 10.5 mmol) were added to a 2.5% acetic acid/methanol (80 mL) solution of 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine (1.00 g, 2.33 mmol). The resulting reaction mixture was stirred at 60 °C for 13 hours and cooled to room temperature. A 1 M aqueous solution of NaOH (50 mL) and dichloromethane (50 mL) were then added, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (50 mL×3). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography (SiO₂, methanol/ethyl acetate = 2:8) to thereby provide 1-(4-ethylbenzyl)-4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine (740 mg, 62%).

[Reference Example 26] Synthesis of 4-[(glycylamino)methyl]-1-(4-methylthiobenzyl)piperidine

[0251] A DMF (4 mL) solution of 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]-1-(4-methylthiobenzyl) piperidine (590 mg) and piperidine (1 mL) was stirred at 60 °C for 2 hours. After concentrating, the obtained crude product was purified by column chromatography (SiO₂,triethylamine/methanol/dichloromethane = 1:1:9) to thereby

afford 4-[(glycylamino)methyl]-1-(4-methylthiobenzyl)piperidine (365 mg) as a white solid. ^{1}H NMR (CDCl₃, 270MHz) δ 1.25 (dd, J = 12 Hz, 4.1 Hz, 2H), 1.34 (dd, J = 12 Hz, 4.1 Hz, 2H), 1.51 (br-s, 2H), 1.66 (d, J = 12 Hz, 2H), 1.77 (d, J = 7.3 Hz, 1H), 1.94 (t, J = 9.5 Hz, 2H), 2.48 (s, 3H), 2.80 (d, J = 12 Hz, 2H), 3.18 (t, J = 6.2 Hz, 2H), 3.35 (s, 2H), 3.45 (s, 2H), 7.18-7.29 (m, 4H), 7.35 (br-s, 1H).

[0252] Further, 1-(4-ethylbenzyl)-4-[(glycylamino)methyl]piperidine was synthesized by using the corresponding starting material and reactants according to the method of Reference Example 26: 333 mg, 79%.

[Reference Example 27] Synthesis of 4-[(glycylamino)methyl]-1-(4-fluorobenzyl)piperidine

[0253] An acetonitrile (200 mL) solution of 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine (1.50 g, 3.49 mmol), 4-fluorobenzyl bromide (0.478 mL, 3.84 mmol) and triethylamine (1.47 mL, 10.5 mmol) was stirred at room temperature for 13 hours. The obtained product was purified by column chromatography (SiO₂, 10% methanol/dichloromethane) to thereby provide 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine. A DMF (5 mL) solution of the 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine and piperidine (5 mL) was further stirred at room temperature for 17 hours. After concentrating, the obtained crude product was purified by column chromatography (SiO₂, triethylamine/methanol/dichloromethane = 0.5:2:8) to afford 4-[(glycylamino)methyl]-1-(4-fluorobenzyl)piperidine (453 mg, 46%).

[Reference Example 28] Synthesis of 4-{(glycylamino)methyl]-1-{4-(N-phenylcarbamoyl)benzyl]piperidine

[0254] An acetonitrile (100 mL) solution of 4-(N-phenylcarbamoyl)benzyl chloride (800 mg, 3.26 mmol) was dropped into a mixture of 4-[[N-(9-fluorenylmethyloxycarbonyl)glycyl]aminomethyl]piperidine (1.27 g, 2.96 mmol) with triethylamine (1.25 mL, 8.88 mmol), KI (50 mg, 0.30 mmol) and acetonitrile (200 mL). The resulting mixture was stirred at room temperature for 19 hours and stirred at 60 °C for another 5 hours. After concentrating, the obtained crude product was purified by column chromatography (SiO₂, 5% methanol/dichloromethane-triethylamine/methanol/dichloromethane = 2:2:96) to provide 4-[(glycylamino)methyl]-1-[4-(N-phenylcarbamoyl)benzyl]piperidine (340 mg, 30%).

[Example 1091] Synthesis of 1-(4-chlorobenzyl)-4-[[N-(3-cyanobenzoyl)valyl]aminomethyl]piperidine (Compd. No. 619)

[0255] Triethylamine (0.011 mL, 0.077 mmol), m-cyanobenzoic acid (28 mg, 0.071 mmol), EDCI (13 mg, 0.065 mmol) and HOBt (9 mg, 0.065 mmol) were added to a dichloromethane (0.60 mL) solution of 1-(4-chlorobenzyl)-4-[(valylamino) methyl]piperidine (20 mg, 0.059 mmol). The resulting reaction mixture was stirred at 25 °C for 16 hours, and the obtained solution was diluted with dichloromethane (0.75 mL), washed with a 2 M aqueous solution of NaOH (0.75 mL \times 2) and dried by filtration through a PTFE membrane. The dried solution was concentrated to thereby afford 1-(4-chlorobenzyl)-4-[[N-(3-cyanobenzoyl)valyl]aminomethyl]piperidine (Compd. No. 619) (24.2 mg, 88%). Further purification was not required for the resulting compound. The purity was determined by RPLC/MS (85%). ESI/MS m/e 467 (M++H, $C_{26}H_{31}ClN_4O_2$).

40 [Examples 1092 to 1543]

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[0256] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1091. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 27.

Table 27

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1092	467	C ₂₂ H ₂₅ BrClN ₃ O ₂	478	11	46
1093	468	C ₂₄ H ₃₁ CIN ₄ O ₂	443	. 9	41
1094	469	C ₂₃ H ₂₈ CIN ₃ O ₃	430	7*	27
1095	470	C ₂₃ H ₂₅ CIN ₄ O ₂	425	21	Q
1096	471	C ₂₄ H ₂₈ CIN ₃ O ₄	458	7	29
1097	472	C ₂₉ H ₃₁ N ₃ O ₃	504	5*	21
1098	473	C ₂₄ H ₂₈ CIN ₃ O ₃	442	16	. 71

Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1099	474	C ₂₃ H ₂₅ CIF ₃ N ₃ O ₂	468	14	60
1100	475	C ₂₅ H ₃₂ ClN ₃ O ₂	442	5	22
1101	476	C ₂₂ H ₂₅ CIN ₄ O ₄	445	4	17
1102	477	C ₂₅ H ₃₂ CIN ₃ O ₃	458	10*	36
1103	478	C ₂₁ H ₂₇ CIN ₄ O ₂	403	9	47
1104	479	C ₂₀ H ₂₄ CIN ₃ O ₃	390	17	87
1105	480	C ₂₀ H ₂₃ BrClN ₃ O ₃	470	23	Q
1106	481	C ₂₀ H ₂₄ CIN ₃ O ₂ S	406	7	33
1107	482	C ₂₁ H ₂₆ CIN ₃ O ₂ S	420	9	45
1108	483	C ₂₁ H ₂₆ CIN ₃ O ₂ S	420	8	40
1109	484	C ₂₄ H ₂₇ ClN ₄ O ₂	439	9*	34
1110	485	C ₂₄ H ₂₄ CIF ₆ N ₃ O ₂	536	13	49
1111	486	C ₂₃ H ₂₅ CIN ₄ O ₂	425	16	74
1112	487	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₂	434	5	24
1113	488	C ₂₂ H ₂₇ CIN ₄ O ₂	415	7	32
1114	489	C ₂₄ H ₂₄ CIF ₆ N ₃ O ₂	536	21	78
1115	490	C ₂₄ H ₃₀ CIN ₃ O ₃	444	8	35
1116	491	C ₂₃ H ₂₄ CIF ₄ N ₃ O ₂	486	19	· 79
1117	492	C ₂₃ H ₂₅ CIF ₃ N ₃ O ₃	484	18	76
1118	493	C ₂₃ H ₂₄ Cl ₂ F ₃ N ₃ O ₂	502	23	92
1119	494	C ₂₃ H ₂₄ CIF ₄ N ₃ O ₂	486	19	79
1120	495	C ₂₃ H ₂₄ CIF ₄ N ₃ O ₂	486	20	83
1121	496	C ₂₃ H ₂₄ CIF ₄ N ₃ O ₂	486	12	48
1122	497	C ₂₅ H ₃₂ CIN ₃ O ₃	458	4	16
1123	498	C ₂₃ H ₂₆ CIF ₃ N ₄ O ₂	483	13	52
1124	499	C ₂₄ H ₃₁ CIN ₄ O ₂	443	8	36
1125	500	C ₂₃ H ₂₈ CIN ₃ O ₃	430	10	48
1126	501	C ₂₂ H ₂₄ BrCIN ₄ O ₄	523	10	39
1127	502	C ₂₂ H ₂₄ CIFN ₄ O ₄	463	4	17
1128	503	C ₂₂ H ₂₄ Cl ₂ N ₄ O ₄	479	12	52
1129	504	C ₂₄ H ₃₀ CIN ₃ O ₄	460	11	43
1130	505	C ₂₂ H ₂₄ BrCIN ₄ O ₄	523	2	8
1131	506	C ₂₀ H ₂₃ CIN ₄ O ₅	435	2	10
1132	507	C ₂₁ H ₂₆ ClN ₃ O ₃	404	9	44
1133	508	C ₂₄ H ₂₆ CIN ₃ O ₂ S	456	1	5
1134	509	C ₂₀ H ₂₃ BrClN ₃ O ₂ S	484	12	48
1135	510	C ₂₂ H ₂₈ CIN ₃ O ₃	418	9	44
1136	511	C ₂₄ H ₃₂ CIN ₃ O ₃	446	9 .	40

Table 27 (continued)

		Table 27 (conti	,		
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1137	512	C ₂₅ H ₂₉ CIN ₄ O ₂	453	10	45
1138	513	C ₂₄ H ₂₈ CIN ₃ O ₃	442	9	41
1139	514	C ₂₆ H ₃₄ CIN ₃ O ₂	456	11	49
1140	515	C ₂₃ H ₂₈ CIN ₃ O ₃	430	5	24
1141	525	C ₂₃ H ₂₈ CIN ₃ O ₄ S	478	20	85
1142	526	C ₂₀ H ₂₄ CIN ₃ O ₃	390	6	31
1143	527	C ₂₀ H ₂₄ CIN ₃ O ₂ S	406	8	39
1144	528	C ₂₅ H ₃₀ CIF ₃ N ₄ O ₄	543	28.2	95
1145	529	C ₂₀ H ₂₃ CIN ₄ O ₄ S	451	9	39
1146	530	C ₃₁ H ₃₃ CIN ₄ O ₂	529	5	17
1147	531	C ₂₁ H ₂₆ CIN ₃ O ₃ S	436	8	37
1148	532	C ₂₂ H ₂₈ CIN ₃ O ₃	418	8	40
1149	533	C ₂₁ H ₂₆ CIN ₃ O ₃	404	6	32
1150	534	C ₂₁ H ₂₅ CIN ₄ O ₅	449	5	20
1151	535	C ₂₂ H ₂₆ CIN ₃ O ₃ S	448	8	37
1152	536	C ₂₃ H ₃₁ CIN ₄ O ₂	431	6	28
1153	537	C ₂₅ H ₃₄ CIN ₃ O ₃	460	8	34
1154	538	C ₂₇ H ₃₀ CIN ₃ O ₃	480	9	36
1155	539	C ₂₂ H ₂₅ CIF ₃ N ₃ O ₃	472	18	75
1156	540	C ₂₅ H ₂₉ CIN ₄ O ₂	453	8	36
1157	541	C ₂₂ H ₂₆ CIN ₅ O ₄	460	2.4	10
1158	542	C ₂₄ H ₃₀ CIN ₃ O ₂	428	4.6*	51
1159	543	C ₂₄ H ₃₀ CIN ₃ O ₂	428	20.6*	71
1160	544	C ₂₂ H ₂₅ CIFN ₃ O ₂	418	15.8*	56
1161	545	C ₂₂ H ₂₄ Cl ₃ N ₃ O ₂	468	7.3*	23
1162	546	C ₂₂ H ₂₄ Cl ₃ N ₃ O ₂	468	17.4*	55
1163	547	C ₂₂ H ₂₄ Cl ₃ N ₃ O ₂	468	14.1*	44
1164	548	C ₂₂ H ₂₄ Cl ₃ N ₃ O ₂	468	6.8*	22
1165	549	C ₂₂ H ₂₄ Cl ₂ N ₄ O ₄	479	5.7*	18
1166	550	C ₂₂ H ₂₄ Cl ₂ N ₄ O ₄	479	18.9*	58
1167	551	C ₂₄ H ₃₀ CIN ₃ O ₂	428	14.2*	49
1168	552	C ₂₄ H ₂₇ CIF ₃ N ₃ O ₂	482	30.6*	94
1169	553	C ₂₅ H ₂₆ CIF ₆ N ₃ O ₂	550	38.0*	Q
1170	554	C ₂₄ H ₂₆ CIFN ₄ O ₂	457	0.9*	3
1171	555	C ₂₄ H ₂₆ Cl ₂ N ₄ O ₂	473	11.1*	35
1172	556	C ₂₅ H ₂₉ CIN ₄ O ₂	453	12.5*	41
1173	559	C ₂₅ H ₂₆ CIF ₆ N ₃ O ₂	550	15	72
1174	560	C ₂₄ H ₂₇ CIN ₄ O ₂	439	12	68

Table 27 (continued)

		Table 27 (COIII	1		
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1175	561	C ₂₃ H ₂₇ BrClN ₃ O ₂	494	14	73
1176	562	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂	448	13	75
1177	563	$C_{25H_{26}CIF_6N_3O_2}$	550	14	66
1178	564	C ₂₅ H ₃₂ CIN ₃ O ₃	458	5	28
1179	565	C ₂₄ H ₂₆ CIF ₄ N ₃ O ₂	500	12	61
1180	566	C ₂₄ H ₂₇ CIF ₃ N ₃ O ₃	498	12	62
1181	567	C ₂₄ H ₂₆ Cl ₂ F ₃ N ₃ O ₂	516	. 12	61
1182	568	C ₂₄ H ₂₆ CIF ₄ N ₃ O ₂	500	15	77
1183	569	C ₂₄ H ₂₆ CIF ₄ N ₃ O ₂	500	11	59
1184	570	C ₂₄ H ₂₆ CIF ₄ N ₃ O ₂	500	16	84
1185	571	C ₂₆ H ₃₄ CIN ₃ O ₃	472	14	77
1186	572	C ₂₄ H ₂₈ ClF ₃ N ₄ O ₂	497	11	55
1187	573	C ₂₁ H ₂₅ BrClN ₃ O ₂ S	500	12	64
1188	574	C ₂₁ H ₂₅ BrClN ₃ O ₂ S	500	15	75
1189	575	C ₂₅ H ₃₄ CIN ₃ O ₃	460	16	87
1190	576	C ₂₂ H ₂₈ CIN ₃ O ₂ S ₂	466	13	71
1191	577	C ₂₂ H ₂₈ CIN ₃ O ₃	418	12	72
1192	578	C ₂₅ H ₂₈ CIN ₃ O ₂ S	470	15	81
1193	579	C ₂₅ H ₂₉ CIN ₄ O ₂	453	17	94
1194	580	C ₂₂ H ₂₈ CIN ₃ O ₂ S	434	15	91
1195	581	C ₂₁ H ₂₆ CIN ₃ O ₂ S	420	13	80
1196	582	C ₂₂ H ₂₈ CIN ₃ O ₂ S	434	10	59
1197	583	C ₂₆ H ₃₁ CIN ₄ O ₂	467	6	31
1198	584	C ₃₀ H ₃₂ CIN ₃ O ₃	518	18	92
1199	585	C ₂₄ H ₂₇ CIN ₄ O ₂	439	14	85
1200	586	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂	448	17	97
1201	587	C ₂₄ H ₂₇ CIF ₃ N ₃ O ₂	482	17	91
1202	588	C ₂₃ H ₂₉ CIN ₄ O ₂	429	5	29
1203	589	C ₂₇ H ₃₆ CIN ₃ O ₂	470	4	24
1204	590	C ₂₆ H ₃₄ CIN ₃ O ₂	456	6	36
1205	591	C ₂₅ H ₃₃ ClN ₄ O ₂	457	7	38
1206	592	C ₂₄ H ₃₀ CIN ₃ O ₃	444	4	20
1207	593	C ₂₄ H ₃₀ CIN ₃ O ₃	444	2	14
1208	594	C ₂₃ H ₂₈ CIN ₃ O ₃	430	4	25
1209	595	C ₂₅ H ₃₀ CIN ₃ O ₄	472	7	38
1210	596	C ₂₅ H ₃₀ CIN ₃ O ₃	456	7	40
1211	597	C ₂₅ H ₃₀ CIN ₃ O ₃	456	15	85
1212	598	C ₂₁ H ₂₆ CIN ₃ O ₃	404	15	94

Table 27 (continued)

Evample	Compd No	Molecular Formula	ESI/MS m/e	Viold (mg)	Viold (9/)
Example	Compd. No.			Yield (mg)	Yield (%)
1213	599	C ₂₂ H ₂₉ CIN ₄ O ₂	417	5	30
1214	600	C ₂₁ H ₂₅ BrClN ₃ O ₃	484	6	34
1215	601	C ₂₄ H ₃₀ CIN ₃ O ₃	444	5	28
1216	602	C ₂₅ H ₃₃ CIN ₄ O ₂	457	5	28
1217	603	C ₂₃ H ₂₉ CIN ₄ O ₂	429	4	22
1218	604	C ₂₁ H ₂₇ CIN ₄ O ₂	403	9	58
1219	605	C ₂₁ H ₂₆ CIN ₃ O ₃	404	17	87
1220	606	C ₂₁ H ₂₆ CIN ₃ O ₂ S	420	15	74
1221	607	C ₂₂ H ₂₈ CIN ₃ O ₃ S	450	31	Q
1222	608	C ₂₃ H ₃₀ CIN ₃ O ₃	432	17	80
1223	609	C ₂₂ H ₂₈ CIN ₃ O ₃	418	18	89
1224	610	C ₂₃ H ₂₈ CIN ₃ O ₃ S	462	20	86.
1225	611	C ₂₆ H ₃₆ CIN ₃ O ₃	474	21	90
1226	612	C ₂₈ H ₃₂ CIN ₃ O ₃	494	20	84
1227	613	C ₂₃ H ₂₇ CIF ₃ N ₃ O ₃	486	19	81
1228	614	C ₂₄ H ₃₃ CIN ₄ O ₂	445	23	Q
1229	615	C ₂₅ H ₂₉ CIN ₄ O ₂	453	4	20
1230	616	C ₃₂ H ₃₅ CIN ₄ O ₂	543	11	40
1231	617	C ₂₅ H ₂₇ CIF ₃ N ₃ O ₂	482	6.7	37
1232	620	C ₂₅ H ₃₁ BrClN ₃ O ₂	520	15	49
1233	621	C ₂₅ H ₃₁ Cl ₂ N ₃ O ₂	476	18	64
1234	622	C ₂₇ H ₃₇ CIN ₄ O ₂	485	14	50
1235	623	C ₂₆ H ₃₄ CIN ₃ O ₃	472	19	69
1236	624	C ₂₅ H ₃₁ CIN ₄ O ₄	487	21	73
1237	625	C ₂₅ H ₃₃ CIN ₄ O ₂	457	19	69
1238	626	C ₂₇ H ₃₀ CIF ₆ N ₃ O ₂	578	8	25
1239	627	C ₂₇ H ₃₆ CIN ₃ O ₃	486	16	55
1240	628	C ₂₇ H ₃₄ CIN ₃ O ₄	500	24	80
1241	629	C ₂₆ H ₃₀ CIF ₄ N ₃ O ₂	528	18	56
1242	630	C ₂₆ H ₃₁ CIF ₃ N ₃ O ₃	526	21	68
1243	631	C ₂₆ H ₃₀ Cl ₂ F ₃ N ₃ O ₂	544	15	48
1244	632	C ₂₆ H ₃₀ CIF ₄ N ₃ O ₂	528	13	41
1245	633	C ₂₆ H ₃₀ CIF ₄ N ₃ O ₂	528	20	63
1246	634	C ₂₆ H ₃₀ CIF ₄ N ₃ O ₂	528	19	62
1247	635	C ₂₈ H ₃₈ CIN ₃ O ₃	500	11	36
1248	636	C ₂₆ H ₃₄ CIN ₃ O ₂	456	21	89
1249	637	C ₂₆ H ₃₁ CIF ₃ N ₃ O ₂	510	20	95
1250	638	C ₂₆ H ₃₁ CIN ₄ O ₂	467	15	54

Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1251	639	C ₂₇ H ₃₇ CIN ₄ O ₂	485	19	66
1252	640	C ₂₆ H ₃₄ CIN ₃ O ₃	472	16	56
1253	641	C ₂₇ H ₃₄ CIN ₃ O ₄	500	18	59
1254	642	C ₃₂ H ₃₆ CIN ₃ O ₃	546	24	73
1255	643	C ₂₆ H ₃₁ CIF ₃ N ₃ O ₂	510	16	54
1256	644	C ₂₉ H ₄₀ ClN ₃ O ₂	498	18	61
1257	645	C ₂₅ H ₃₃ CIN ₄ O ₂	457	22	78
1258	646	C ₂₆ H ₃₄ CIN ₃ O ₃	472	13	47
1259	647	C ₂₇ H ₃₄ ClN ₃ O ₃	500	13	46
1260	648	C ₂₈ H ₃₈ CIN ₃ O ₂	484	17	60
1261	649	C ₂₈ H ₃₈ CIN ₃ O ₃	500	12.5	42
1262	650	C ₃₂ H ₃₆ CIN ₃ O ₃	546	1*	2
1263	651	C ₂₈ H ₃₅ CIN ₄ O ₂	495	4*	12
1264	652	C ₂₅ H ₃₁ CIN ₄ O ₄	487	5*	14
1265	653	C ₃₀ H ₄₂ CIN ₃ O ₃	528	1*	3
1266	654	C ₂₇ H ₃₄ CIN ₃ O ₃	484	7*	21
1267	655	C ₂₆ H ₃₂ CIF ₃ N ₄ O ₂	525	6*	16
1268	656	C ₂₃ H ₃₀ CIN ₃ O ₃	432	6*	18
1269	657	C ₂₃ H ₃₀ CIN ₃ O ₂ S	448	4*	13
1270	658	C ₂₇ H ₃₃ CIN ₄ O ₂	48	1*	4
1271	659	C ₂₃ H ₂₉ CIN ₄ O ₄ S	493	4*	10
1272	660	C ₃₄ H ₃₉ CIN ₄ O ₂	571	3*	7
1273	661	C ₂₄ H ₃₂ CIN ₃ O ₃ S	478	3*	7
1274	662	C ₂₅ H ₃₄ ClN ₃ O ₃	460	2*	6
1275	663	C ₂₄ H ₃₂ ClN ₃ O ₃	446	2*	5
1276	664	C ₂₄ H ₃₁ ClN ₄ O ₅	491	2*	. 5
1277	665	C ₂₅ H ₃₂ CIN ₃ O ₃ S	490	1*	3
1278	666	C ₂₆ H ₃₇ CIN ₄ O ₂	473	3*	7
1279	667	C ₃₀ H ₃₆ ClN ₃ O ₃	522	3*	7
1280	668	C ₂₅ H ₃₁ CIF ₃ N ₃ O ₃	514	2*	6
1281	669	C ₂₄ H ₃₃ CIN ₄ O ₂	445	15*	45
1282	670	C ₂₃ H ₂₉ BrClN ₃ O ₃	510	3*	7
1283	671	C ₂₃ H ₂₉ CIN ₄ O ₅	477	2*	5
1284	672	C ₂₃ H ₃₁ CIN ₄ O ₂	431	2*	7
1285	673	C ₂₃ H ₃₀ ClN ₃ O ₂ S	448	. 2*	6
1286	674	C ₂₄ H ₃₂ CIN ₃ O ₂ S	462	3*	9
1287	675	C ₂₄ H ₃₂ CIN ₃ O ₂ S	462	1*	4
1288	676	C ₂₇ H ₃₃ ClN ₄ O ₂	482	2*	6

Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1289	677	C ₂₈ H ₃₅ CIN ₄ O ₂	495	2*	6
1290	678	C ₂₄ H ₃₂ CIN ₃ O ₃	446	3*	9
1291	679	C ₂₇ H ₃₂ CIN ₃ O ₂ S	498	1*	3
1292	680	C ₂₃ H ₂₉ BrCIN ₃ O ₂ S	526	2*	6
1293	681	C ₂₅ H ₃₄ CIN ₃ O ₃	460	2*.	5
1294	682	C ₂₇ H ₃₈ CIN ₃ O ₃	488	2*	4
1295	683	C ₂₄ H ₃₂ CIN ₃ O ₂ S ₂	494	1*	4
1296	684	C ₂₆ H ₃₆ CIN ₃ O ₄ S ₂	554	2*	5
1297	685	C ₂₄ H ₃₂ CIN ₃ O ₄ S ₂	526	3*	7
1298	687	C ₂₅ H ₃₀ CIN ₃ O ₂	440	24	Q.
1299	688	C ₂₇ H ₂₈ CIF ₆ N ₃ O ₂	576	28	98
1300	689	C ₂₆ H ₂₉ CIN ₄ O ₂	465	23	99
1301	690	C ₂₅ H ₂₉ BrClN ₃ O ₂	518	26	99
1302	691	C ₂₇ H ₃₅ CIN ₄ O ₂	483	24	97
1303	692	C ₂₆ H ₃₂ CIN ₃ O ₃	470	24	Q
1304	693	C ₂₇ H ₂₈ CIF ₆ N ₃ O ₂	576	16	55
1305	694	C ₂₇ H ₃₄ ClN ₃ O ₃	484	25	Q
1306	695	C ₂₇ H ₃₂ CIN ₃ O ₄	498	12	47
1307	696	C ₂₆ H ₂₉ CIF ₃ N ₃ O ₃	524	25	95
1308	697	C ₂₆ H ₂₉ CIN ₄ O ₂	465	15	64
1309	698	C ₂₇ H ₃₅ CIN ₄ O ₂	483	24	Q
1310	699	C ₂₆ H ₃₂ CIN ₃ O ₃	470	26	Q
1311	700	C ₂₇ H ₃₂ CIN ₃ O ₄	498	15	62
1312	701	C ₂₇ H ₃₂ CIN ₃ O ₃	482	11	44
1313	702	C ₂₆ H ₂₉ CIF ₃ N ₃ O ₂	508	23	94
1314	703	C ₂₈ H ₃₆ CIN ₃ O ₂	482	26	Q
1315	704	C ₂₅ H ₂₉ CIN ₄ O ₄	485	11	43
1316	705	C ₂₄ H ₃₀ ClN ₃ O ₂ S	460	25	Q
1317	706	C ₂₄ H ₃₀ ClN ₃ O ₂ S	460	25	Q
1318	707	C ₂₆ H ₂₉ CIF ₃ N ₃ O ₂	508	15	55
1319	708	C ₂₃ H ₂₇ BrCIN ₃ O ₂ S	526	25	92
1320	709	C ₂₄ H ₃₀ CIN ₃ O ₂ S ₂	492	26	Q
1321	710	C ₂₃ H ₂₇ BrCIN ₃ O ₂ S	526	25	94
1322	711	C ₂₅ H ₃₂ CIN ₃ O ₃	458	26	Q
1323	712	C ₂₇ H ₃₀ ClN ₃ O ₂ S	496	26	Q
1324	713	C ₂₄ H ₃₀ CIN ₃ O ₃	444	26	Q
1325	714	C ₂₈ H ₃₃ CIN ₄ O ₂	493	12	50
1326	715	C ₂₃ H ₂₈ CIN ₃ O ₂ S	446	24	Q

Table 27 (continued)

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Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1327	716	C ₂₇ H ₃₁ CIN ₄ O ₂	479	32	Q
1328	717	C ₂₃ H ₂₇ CIN ₄ O ₅	475	23	95
1329	718	C ₂₃ H ₂₉ CIN ₄ O ₂	429	. 24	Q
1330	719	C ₂₃ H ₂₈ CIN ₃ O ₃	430	24	Q
1331	720	C ₂₃ H ₂₇ BrClN ₃ O ₃	510	24	95
1332	721	C ₂₄ H ₃₁ CIN ₄ O ₂	443	22	98
1333	722	C ₂₆ H ₃₂ CIN ₃ O ₃	470	9	37
1334	723	C ₂₅ H ₃₁ CIN ₄ O ₂	455	10	44
1335	724	C ₂₉ H ₃₈ ClN ₃ O ₂	496	28	Q
1336	725	C ₃₂ H ₃₄ CIN ₃ O ₃	544	26	95
1337	726	C ₂₇ H ₃₃ CIN ₄ O ₃	497	3	11
1338	727	C ₂₅ H ₂₉ Cl ₂ N ₃ O ₂	474	25	Q
1339	728	C ₂₅ H ₃₁ CIN ₄ O ₂	455	21	92
1340	729	C ₂₅ H ₂₉ CIN ₄ O ₄	485	26	Q
1341	730	C ₂₅ H ₂₉ Cl ₂ N ₃ O ₂	474	21	90
1342	731	C ₂₇ H ₃₂ CIN ₃ O ₃	482	10	41
1343	732	C ₂₆ H ₂₈ CIF ₄ N ₃ O ₂	526	27	Q
1344	733	C ₂₈ H ₃₆ CIN ₃ O ₃	498	22	89
1345	734	C ₂₆ H ₂₈ CIF ₄ N ₃ O ₂	526	25	94
1346	735	C ₂₆ H ₂₈ CIF ₄ N ₃ O ₂	526	23	87
1347	736	C ₂₆ H ₃₀ CIF ₃ N ₄ O ₂	523	24	78
1348	737	C ₂₆ H ₂₈ CIF ₄ N ₃ O ₂	526	21	66
1349	738	C ₂₅ H ₃₂ ClN ₃ O ₃	458	23	84
1350	739	C ₂₇ H ₃₁ ClN ₄ O ₂	479	19	66
1351	740	C ₂₄ H ₃₁ CIN ₄ O ₅	489	23	77
1352	741	C ₂₃ H ₂₇ CIN ₄ O ₄ S	491	26	88
1353	742	C ₂₄ H ₃₀ CIN ₃ O ₃ S	476	23	82
1354	743	C ₂₃ H ₂₈ CIN ₃ O ₃	430	21	81
1355	744	C ₂₆ H ₃₂ CIN ₃ O ₂	454	25	91
1356	745	C ₂₇ H ₃₆ CIN ₃ O ₃	486	23	80
. 1357	746	C ₂₆ H ₃₅ CIN ₄ O ₂	471	27	96
1358	747	C ₂₅ H ₂₉ CIF ₃ N ₃ O ₃	512	23	74
1359	748	C ₂₃ H ₂₈ CIN ₃ O ₂ S	446	22	82
1360	751	C ₂₄ H ₃₀ CIN ₃ O ₃	444	3	11
1361	752	C ₂₅ H ₂₆ CIF ₆ N ₃ O ₃	566	7	20
1362	753	C ₂₄ H ₂₇ CIN ₄ O ₃	455	6	22
1363	754	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₃	464	8	29
1364	755	C ₂₄ H ₃₀ CIN ₃ O ₄	460	6	22

Table 27 (continued)

L	Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
	1365	756	C ₂₃ H ₂₇ CIN ₄ O ₅	475	5	18
L	1366	757	C ₂₅ H ₃₂ CIN ₃ O ₄	474	5	18
	1367	758	$C_{25}H_{30}CIN_3O_5$	488	5	18
	1368	759	C ₂₄ H ₂₇ CIF ₃ N ₃ O ₄	514	6	20
Γ	1369	760	C ₂₄ H ₂₆ CIF ₄ N ₃ O ₃	516	6	18
$\cdot \Gamma$	1370	761	C ₂₄ H ₂₆ CIF ₄ N ₃ O ₃	516	3	10
Γ	1371	762	C ₂₄ H ₂₇ CIF ₃ N ₃ O ₃	498	2	95
Γ	1372	763	C ₂₃ H ₂₈ CIN ₃ O ₃	430	4	95
	1373	764	C ₂₄ H ₃₀ CIN ₃ O ₂	428	9	42
	1374	765	C ₂₅ H ₃₂ CIN ₃ O ₂	442	10	47
Γ	1375	766	C ₂₅ H ₂₉ CIF ₃ N ₃ O ₂	496	10	42
Γ	1376	767	C ₂₅ H ₃₂ CIN ₃ O ₄ S	506	8	32
Γ	1377	768	C ₂₄ H ₂₉ BrClN ₃ O ₂	506	9	35
	1378	769	C ₂₅ H ₂₉ CIF ₃ N ₃ O ₃	512	6	22
Γ	1379	770	C ₂₅ H ₂₈ CIF ₄ N ₃ O ₂	514	3	10
T	1380	771	C ₂₅ H ₂₈ CIF ₄ N ₃ O ₂	514	10	. 37
Γ	1381	772	C ₂₅ H ₂₉ CIF ₃ N ₃ O ₂	496	8	33
	1382	773	C ₂₆ H ₃₆ ClN ₃ O ₃	474	10	41
	1383	774	C ₂₃ H ₃₀ CIN ₃ O ₂ S ₂	480	12	50
	1384	775	C ₂₇ H ₃₈ CIN ₃ O ₃	488	14	57
	1385	776	C ₂₉ H ₃₄ CIN ₃ O ₃	508	12	49
	1386	777	C ₂₄ H ₂₉ CIF ₃ N ₃ O ₃	500	22	87
	1387	778	C ₂₄ H ₂₈ Cl ₂ N ₄ O ₄	507	6	22
	1388	779	C ₂₄ H ₂₉ Cl ₂ N ₃ O ₂	462	10	46
	1389	780	C ₂₄ H ₂₉ CIN ₄ O ₄	473	15	65
	1390 1390	781 781	C ₂₆ H ₃₁ CIN ₄ O ₂	467 467	7*	20 20
	1391	782	C ₂₅ H ₃₂ CIN ₃ O ₃	458	8*	23
	1392	783	C ₂₆ H ₃₄ CIN ₃ O ₃	472	7*	19
Γ	1393	784	C ₂₆ H ₃₁ CIF ₃ N ₃ O ₂	510	7*	17
	1394	785	C ₂₆ H ₃₄ CIN ₃ O ₄	488	6*	17
	1395	786	C ₂₄ H ₂₈ CIN ₃ O ₂	426	22	. 9
Γ	1396	787	C ₂₅ H ₃₀ CIN ₃ O ₂	440	21	94
	1397	788	C ₂₅ H ₂₇ CIF ₃ N ₃ O ₂	494	4*	14
	1398	789	C ₂₅ H ₃₀ CIN ₃ O ₄ S	504	9	35
	1399	790	C ₂₄ H ₂₇ Cl ₂ N ₃ O ₂	460	5*	16
	1400	791	C ₂₄ H ₂₇ CIN ₄ O ₄	471	3*	10
	1401	792	C ₂₅ H ₂₇ CIF ₃ N ₃ O ₃	510	5*	16
Γ	1402	793	C ₂₅ H ₂₆ CIF ₄ N ₃ O ₂	511	5*	16

Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Viold (mg)	Viold (9/)
<u>_</u>				Yield (mg) 5*	Yield (%)
1403	794	C ₂₅ H ₂₆ CIF ₄ N ₃ O ₂	512		16
1404	795	C ₂₅ H ₂₇ CIF ₃ N ₃ O ₂	494	6*	21
1405	796	C ₂₃ H ₂₈ CIN ₃ O ₂ S ₂	478	4*	14
1406	797	C ₂₁ H ₃₆ CIN ₃ O ₃	486	7*	29
1407	798	C ₂₉ H ₃₂ CIN ₃ O ₃	506	3	13
1408	799	C ₂₄ H ₂₇ CIF ₃ N ₃ O ₃	498	3*	11
1409	800	C ₂₄ H ₂₆ Cl ₂ N ₄ O ₄	505	5*	15
1410	801	C ₂₆ H ₂₉ CIN ₄ O ₂	465	12	41
1411	802	C ₂₅ H ₃₀ CIN ₃ O ₃	456	5*	15
1412	803	C ₂₆ H ₃₂ CIN ₃ O ₃	470	6*	16
1413	804	C ₂₆ H ₂₉ CIF ₃ N ₃ O ₂	508	8*	20
1414	805	C ₂₆ H ₃₂ ClN ₃ O ₄	486	6*	15
1415	806	C ₂₄ H ₂₇ BrCIN ₃ O ₂	506	5 *	14
1416	807	C ₂₇ H ₃₂ CIN ₅ O ₃	510	29.7	Q
1417	808	C ₂₆ H ₃₃ CIN ₄ O ₃	485	29.9	Q
1418	809	C ₂₅ H ₃₀ Cl ₂ N ₄ O ₃	505	30.2	Q
1419	810	C ₃₀ H ₃₅ CIN ₄ O ₄	551	31.0	Q
1420	811	C ₂₅ H ₂₉ Cl ₂ N ₅ O ₅	550	30.4	Q
1421	812	C ₂₄ H ₃₁ ClN ₄ O ₃ S ₂	523	25.0	88
1422	813	C ₂₆ H ₃₀ CIF ₃ N ₄ O ₃	539	20.5	70
1423	814	C ₂₆ H ₃₀ CIF ₃ N ₄ O ₄	555	22.7	75
1424	815	C ₂₆ H ₂₉ CIF ₄ N ₄ O ₃	557	25.8	85
1425	816	C ₂₆ H ₃₀ CIF ₃ N ₄ O ₃	539	25.3	86
1426	817	C ₂₆ H ₂₉ CIF ₄ N ₄ O ₃	557	26.8	88
1427	818	C ₂₅ H ₃₀ BrClN ₄ O ₃	551	27.1	90
1428	819	C ₂₇ H ₂₉ CIF ₆ N ₄ O ₃	607	13.9	42
1429	820	C ₂₅ H ₃₀ CIN ₅ O ₅	516	14.1	51
1430	821	C ₂₄ H ₂₈ Cl ₂ N ₄ O ₅	523	40	86
1431	822	C ₂₃ H ₃₀ CIN ₃ O ₃ S ₂	496	41	93
1432	823	C ₂₆ H ₃₁ CIN ₄ O ₃	483	43	Q
1433	824	C ₂₇ H ₃₈ CIN ₃ O ₄	503	37	83
1434	825	C ₂₉ H ₃₄ CIN ₃ O ₄	524	28	61
1435	826	C ₂₄ H ₂₉ CIF ₃ N ₃ O ₄	516	40	87
1436	827	C ₂₆ H ₃₁ CIN ₄ O ₃	483	31	72
1437	828	C ₂₅ H ₂₉ CIF ₃ N ₃ O ₄	528	40	86
1438	829	C ₂₅ H ₂₈ CIF ₄ N ₃ O ₃	530	45	97
1439	830	C ₂₅ H ₂₈ CIF ₄ N ₃ O ₃	530	35	74
1440	831	C ₂₄ H ₂₉ BrClN ₃ O ₃	523	45	98

Table 27 (continued)

Evample	Compd No	Molecular Formula	ESI/MS m/s	Viold (ma)	Viold (9/)
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1441	832	C ₂₄ H ₂₉ Cl ₂ N ₃ O ₃	478	38	91
1442	833	C ₂₄ H ₂₉ CIN ₄ O ₅	488	38	87
1443	834	C ₂₅ H ₂₉ CIF ₃ N ₃ O ₃	512	42	93
1444	835	C ₂₄ H ₃₀ CIN ₃ O ₃	444	43	Q
1445	836	C ₂₅ H ₃₂ CIN ₃ O ₃	458	37	91
1446	837	C ₂₅ H ₂₉ CIF ₃ N ₃ O ₃	512	41	91
1447	838	C ₂₆ H ₃₄ CIN ₃ O ₄	488	34	78
1448	839	C ₂₇ H ₃₆ CIN ₃ O ₆	534	37	71
1449	942	C ₂₇ H ₃₀ CIF ₆ N ₃ O ₂	578	17	48
1450	997	C ₂₆ H ₃₄ CIN ₃ O ₂	456	7.6*	23
1451	998	C ₂₇ H ₃₃ CIF ₃ N ₃ O ₂	524	6	15
1452	999	C ₂₇ H ₃₆ CIN ₃ O ₂	470	8	24
1453	1000	C ₂₇ H ₃₆ CIN ₃ O ₃	486	9	24
1454	1001	C ₂₈ H ₃₈ CIN ₃ O ₃	500	4	10
1455	1002	C ₂₇ H ₃₃ CIF ₃ N ₃ O ₃	540	9	23
1456	1003	C ₂₈ H ₃₈ CIN ₃ O ₂	484	7	21
1457	1004	C ₂₈ H ₃₈ CIN ₃ O ₄	516	11	30
1458	1005	C ₂₉ H ₄₀ CIN ₃ O ₅	547	9	23
1459	1006	C ₃₀ H ₄₂ CIN ₃ O ₄	544	8	21
1460	1007	C ₃₂ H ₄₆ CIN ₃ O ₅	589	7	17
1461	1008	C ₂₅ H ₃₁ CIN ₄ O ₃	471	25	79
1462	1009	C ₂₆ H ₃₃ CIN ₄ O ₄	501	35	97
1463	1010	C ₂₇ H ₃₅ CIN ₄ O ₄	515	35	9
1464	1011	C ₂₇ H ₃₅ CIN ₄ O ₃	499	32	54
1465	1012	C ₂₇ H ₃₅ CIN ₄ O ₅	531	27	77
1466	1013	C ₂₈ H ₃₇ CIN ₄ O ₆	561	14	37
1467	1014	C ₂₉ H ₃₉ CIN ₄ O ₅	559	24	66
1468	1015	C ₃₁ H ₄₃ CIN ₄ O ₆	603	25	65
1469	1018	C ₂₆ H ₃₄ CIN ₃ O ₄	488	13.0*	39
1470	1019	C ₂₈ H ₃₈ CIN ₃ O ₅	532	13.4*	37
1471	1020	C ₂₅ H ₃₂ CIN ₃ O ₄	474	12.7*	40
1472	1021	C ₂₆ H ₂₈ CIF ₆ N ₃ O ₄	596	13.8*	34
1473	1022	C ₂₅ H ₃₂ CIN ₃ O ₄	474	14.2*	37
1474	1023	C ₂₅ H ₃₂ CIN ₃ O ₂	442	11.5*	32
1475	1024	C ₂₆ H ₃₄ CIN ₃ O ₅	504	12.0*	30
1476	1025	C ₂₇ H ₃₆ CIN ₃ O ₄	502	14.7*	37
1477	1026	C ₂₉ H ₄₀ CIN ₃ O ₅	546	13.5*	32
1478	1027	C ₂₆ H ₃₄ CIN ₃ O ₄	488	11.9*	31

Table 27 (continued)

		Table 27 (Conti			
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1479	1028	C ₂₇ H ₃₀ CIF ₆ N ₃ O ₄	610	14.6*	31
1480	1029	C ₂₅ H ₃₂ CIN ₃ O ₃	458	14.0*	38
1481	1030	C ₂₄ H ₂₇ CIF ₃ N ₃ O ₃	498	14.0*	35
1482	1031	C ₂₄ H ₃₀ CIN ₃ O ₃	444	10.4*	29
1483	1032	C ₂₅ H ₃₂ CIN ₃ O ₄	474	14.9*	39
1484	1033	C ₂₅ H ₃₂ ClN ₃ O ₂	442	13.3*	37
1485	1034	C ₂₆ H ₃₄ CIN ₃ O ₅	504	13.7*	34
1486	1035	C ₂₇ H ₃₆ CIN ₃ O ₄	502	16.7*	42
1487	1036	C ₂₉ H ₄₀ CIN ₃ O ₅	547	15.5*	36
1488	1037	C ₂₆ H ₃₄ CIN ₃ O ₄	488	14.1*	36
1489	1038	C ₂₇ H ₃₀ CIF ₆ N ₃ O ₄	610	17.5*	37
1490	1039	C ₂₅ H ₃₂ CIN ₃ O ₃	458	15.1*	41
1491	1040	C ₂₄ H ₂₇ CIF ₃ N ₃ O ₃	498	15.4*	39
1492	1041	C ₂₄ H ₃₀ CIN ₃ O ₃	444	12.7*	35
1493	1042	C ₂₂ H ₂₆ BrCIN ₄ O ₂	495	10.4*	25
1494	1043	C ₂₂ H ₂₆ Cl ₂ N ₄ O ₂	449	11.1*	29
1495	1044	C ₂₃ H ₂₉ CIN ₄ O ₂	429	5.2*	14
1496	1045	C ₂₃ H ₂₉ ClN ₄ O ₃	445	12.4*	33
1497	1046	C ₂₂ H ₂₅ Cl ₃ N ₄ O ₂	483	10.0*	25
1498	1047	C ₂₄ H ₃₁ CIN ₄ O ₂	443	12.1*	32
1499	1048	C ₂₅ H ₃₃ ClN ₄ O ₅	505	16.1*	39
1500	1049	C ₂₃ H ₂₈ BrCIN ₄ O ₂	507	12.0*	29
1501	1050	C ₂₈ H ₃₈ ClN ₃ O ₄	516	39.2*	Q
1502	1051	C ₂₈ H ₃₈ CIN ₃ O ₂	484	34.0*	Q
1503	1052	C ₂₉ H ₄₀ CIN ₃ O ₅	546	14.5*	39
1504	1053	C ₃₀ H ₄₂ CIN ₃ O ₄	544	11.8*	32
1505	1054	C ₃₂ H ₄₆ CIN ₃ O ₅	588	12.2*	31
1506	1055	C ₂₉ H ₄₀ CIN ₃ O ₄	530	44.5*	Q
1507	1056	C ₃₀ H ₃₆ CIF ₆ N ₃ O ₄	652	46.0*	Q
1508	1057	C ₂₈ H ₃₈ CIN ₃ O ₃	500	11.2*	Q
1509	1058	C ₂₇ H ₃₆ ClN ₃ O ₃	486	35.5*	Q
1510	1059	C ₂₇ H ₃₃ CIF ₃ N ₃ O ₃	540	41.4*	Q
1511	1060	C ₂₉ H ₄₀ CIN ₃ O ₄	530	13.6*	37
1512	1061	C ₃₀ H ₃₆ CIF ₆ N ₃ O ₄	652	44.2*	Q
1513	1062	C ₂₈ H ₃₈ CIN ₃ O ₃	500	39.9*	Q
1514	1063	C ₂₇ H ₃₆ CIN ₃ O ₃	486	12.0*	35
1515	1064	C ₂₇ H ₃₃ CIF ₃ N ₃ O ₃	540	37.8*	Q
1516	1065	C ₂₈ H ₃₈ CIN ₃ O ₄	516	12.3*	34

Table 27 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%
1517	1066	C ₂₈ H ₃₈ CIN ₃ O ₂	484	30.7*	90
1518	1067	C ₂₉ H ₄₀ CIN ₃ O ₅	546	13.8*	37
1519	1068	C ₃₀ H ₄₂ CIN ₃ O ₄	544	13.1*	35
1520	1069	C ₃₂ H ₄₆ CIN ₃ O ₅	589	14.1*	35
1521	1070	C ₂₉ H ₃₄ CIN ₃ O ₃ S ₂	572	38.3	93
1522	1071	C ₃₂ H ₃₅ CIN ₄ O ₃	559	39.6	98
1523	1072	C ₃₃ H ₄₂ CIN ₃ O ₄	580	40.9	98
1524	1073	C ₃₅ H ₃₈ CIN ₃ O ₄	600	40.5	94
1525	1074	C ₃₀ H ₃₃ CIF ₃ N ₃ O ₄	592	38.7	91
1526	1075	C ₃₁ H ₃₃ CIF ₃ N ₃ O ₄	604	38	87
1527	1076	C ₃₀ H ₃₃ CIN ₄ O ₅	565	38.5	94
1528	1077	C ₃₁ H ₃₃ CIF ₃ N ₃ O ₃	588	35.8	84
1529	1078	C ₃₀ H ₃₄ CIN ₃ O ₃	520	34.7	93
1530	1079	C ₃₁ H ₃₆ CIN ₃ O ₃	534	38.4	Q
1531	1080	C ₃₂ H ₃₈ CIN ₃ O ₄	564	39.3	97
1532	1081	C ₃₃ H ₄₀ CIN ₃ O ₆	610	45.5	Q
1533	1082	C ₂₈ H ₃₆ CIN ₃ O ₃	498	4.1*	10
1534	1083	C ₂₈ H ₃₆ CIN ₃ O ₃	498	6.4*	16
1535	1125	C ₃₀ H ₃₂ Cl ₂ N ₄ O ₅	599	3.4*	8
1536	1126	C ₃₀ H ₃₂ BrCIN ₄ O ₅	644	3.4*	7
1537	1127	C ₃₂ H ₃₅ CIN ₄ O ₃	559 ·	1.6*	4
1538	1128	C ₃₁ H ₃₂ CIF ₄ N ₃ O ₃	606	4.3*	10
1539	1129	C ₃₁ H ₃₂ CIF ₄ N ₃ O ₃	606	5.9*	14
1540	1130	C ₃₀ H ₃₃ BrClN ₃ O ₃	599	5.7*	13
1541	1131	C ₃₀ H ₃₃ Cl ₂ N ₃ O ₃	554	6.4*	16
1542	1132 .	C ₃₁ H ₃₃ CIF ₃ N ₃ O ₃	588	6.3*	15
1543	1167	C ₂₇ H ₃₄ CIN ₃ O ₃	484	1.8*	4

[Example 1544] Synthesis of 1-(4-chlorobenzyl)-4-[[N-(3,5-bis(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 1213)

[0257] A dichloromethane (1 mL) solution of 3,5-bis(trifluoromethyl)benzoyl chloride (0.058 mmol) was added to a mixture of 1-(4-chlorobenzyl)-4-[(glycylamino)methyl]piperidine (0.050 mmol) with chloroform (0.2 mL), a piperidinomethylpolystyrene (58 mg) and dichloromethane (0.75 mL). The resulting reaction mixture was stirred at room temperature for 2 hours, and methanol (1.0 mL) was then added to the obtained mixture. The resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was loaded onto a Varian™ SCX column and washed with methanol (16 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (6 mL) and concentrated to thereby provide 1-(4-chlorobenzyl)-4-[[N-(3,5-bis(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 1213) (24.0 mg, 90%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 536.2 (M++H, C₂₄H₂₄CIF₆N₃O₂).

[Examples 1545 to 1547]

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[0258] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1544. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 28.

Table 28

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1545	1214	C ₂₃ H ₂₄ CIF ₄ N ₃ O ₃	486.2	22.2	91
1546	1215	C ₂₂ H ₂₄ Cl ₃ N ₃ O ₂	467.9	20.9	89
1547	1216	C ₂₂ H ₂₄ CIF ₂ N ₃ O ₂	436.0	19.3	89

[Example 1548] Synthesis of 4-[[N-(3-bromo-4-methylbenzoyl)glycyl]aminomethyl]-1-(4-chlorobenzyl)piperidine (Compd. No. 1113)

[0259] 3-Bromo-4-methylbenzoic acid (0.060 mmol), diisopropylcarbodiimide (0.060 mmol) and HOBt (0.060 mmol) were added to a solution of 1-(4-chlorobenzyl)-4-[(glycylamino)methyl]piperidine (0.050 mmol) in chloroform (1.35 mL) and tert-butanol (0.15 mL). The resulting reaction mixture was stirred at room temperature for 15 hours. The mixture was then loaded onto a Varian™ SCX column and washed with methanel/chloroform = 1:1 (12 mL) and methanol (12 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃(5 mL) and concentrated to thereby afford 4-[[N-(3-bromo-4-methylbenzoyl)glycyl]aminomethyl]-1-(4-chlorobenzyl)piperidine (Compd. No. 1113) (16.1 mg, 65%). The purity was determined by RPLC/MS (95%). ESI/MS m/e 494.0 (C₂₃H₂₇BrClN₃O₂).

[Examples 1549 to 1619]

[0260] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of 1548. The obtained products, if necessary, were purified by preparative TLC to provide the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 29

[0261] Compd. No. 1422 was obtained as a by-product of Compd. No. 1418: 5.6 mg, yield: 25%; ESI/MS m/e 447.2 ($C_{22}H_{27}CIN_4O_2S$).

Table 29

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1549	1114	C ₂₂ H ₂₄ BrCIFN ₃ O ₂	498.0	20.2	81
1550	1115	C ₂₂ H ₂₄ Cl ₂ FN ₃ O ₂	452.2	18.6	82
1551	1116	C ₂₃ H ₂₇ CIIN ₃ O ₂	539.1	21.9	81
1552	1117	C ₂₃ H ₂₇ CIN ₄ O ₄	459.2	18.7	81
1553	1187	C ₂₃ H ₂₇ BrCIN ₃ O ₂	494.0	22.1	90
1554	1188	C ₂₄ H ₂₇ CIN ₄ O ₃	455.2	17.2	76
1555	1189	C ₂₅ H ₂₉ CIN ₄ O ₃	469.2	21.1	90
1556	1190	C ₂₂ H ₂₆ CIFN ₄ O ₂	433.2	20.4	94
1557	1241	$C_{23}H_{24}CI_2F_3N_3O_2$	502.0	22.5	90
1558	1242	C ₂₃ H ₂₇ CIFN ₃ O ₂	432.2	21.2	98
1559	1243	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂	448.0	21.6	96
1560	1244	C ₂₂ H ₂₆ CIIN ₄ O ₂	541.0	26.4	98
1561	1245	C ₂₂ H ₂₅ CIF ₂ N ₄ O ₂	451.0	21.3	94
1562	1246	C ₂₁ H ₂₇ CIN ₄ O ₂	403.2	19.4	96
1563	1247	C ₂₈ H ₃₀ CIN ₃ O ₂ S	524.0	24.7	94

Table 29 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1564	1248	C ₂₂ H ₂₅ CIN ₄ O ₅	461.0	20.7	90
1565	1282	C ₂₅ H ₂₆ CIF ₃ N ₄ O ₃	523.2	25.0	96
1566	1283	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₃	464.2	12.2	53
1567	1284	C ₂₂ H ₂₅ BrClN ₃ O ₃	496.0	24.1	97
1568	1285	C ₂₂ H ₂₅ Cl ₂ N ₃ O ₃	450.2	21.8	97
1569	1342	C ₂₂ H ₂₄ BrCl ₂ N ₃ O ₂	514.0	27.2	Q
1570	1343	C ₂₃ H ₂₇ Cl ₂ N ₃ O ₂	448.0	21.4	95
1571	1344	C ₂₂ H ₂₄ Cl ₂ IN ₃ O ₂	560.0	27.0	96
1572	1345	C ₂₃ H ₂₈ CIN ₃ O ₂	430.2	23.8	Q
1573	1346	C ₂₂ H ₂₅ CIIN ₃ O ₃	542.0	29.4	Q
1574	1350	C ₂₁ H ₂₆ CIN ₃ O ₂ S	420.0	13.0	62
1575	1354	C ₂₄ H ₂₈ BrClN ₄ O ₃	537.2	5.2	19
1576	1358	C ₂₃ H ₂₆ CIN ₅ O ₂	. 440.2	21.8	99
1577	1383	C ₂₃ H ₂₄ Cl ₂ F ₃ N ₃ O ₂	502.0	20.0	80
1578	1384	C ₂₀ H ₂₃ BrClN ₃ O ₂ S	486.0	21.0	87
1579	1385	C ₂₈ H ₃₀ CIN ₃ O ₄ S	540.2	23.8	88
1580	1386	C ₂₈ H ₃₀ CIN ₃ O ₂	476.0	20.0	84
1581	1414	C ₂₄ H ₂₈ Cl ₂ N ₄ O ₃	491.0	0.8	3
1582	1418	C ₂₃ H ₂₆ CIN ₅ O ₂ S	472.0	10.4	44
1583	1436	C ₂₉ H ₃₀ CIN ₃ O ₃	504.2	26.8	Q
1584	1600	C ₂₃ H ₂₆ CIF ₃ N ₄ O ₂	483.2	16.5	68
1585	1601	C ₂₃ H ₂₆ CIF ₃ N ₄ O ₃	499.0	20.0	80
1586	1602	C ₂₁ H ₂₄ BrClN ₄ O ₂	481.0	18.1	75
1587	1603	C ₂₁ H ₂₄ Cl ₂ N ₄ O ₂	435.0	5.5	25
1588	1604	C ₂₇ H ₃₀ CIN ₃ O ₃	492.0	18.6	76
1589	1605	C ₂₁ H ₂₇ CIN ₄ O ₂	415.2	18.1	87
1590	1609	C ₂₃ H ₂₅ N ₃ O ₂ S	500.0	18.3	73
1591	1659	C ₂₂ H ₂₆ Cl ₂ N ₄ O ₂	449.0	366.0	83
1592	1664	C ₂₄ H ₂₉ F ₃ N ₄ O ₂ S	495.2	13.7	55
1593	1665	C ₂₄ H ₂₉ F ₃ N ₄ O ₃ S	511.2	14.9	58
1594	1666	C ₂₃ H ₂₈ F ₂ N ₄ O ₂ S	463.2	12.9	56
1595	1667	C ₂₂ H ₂₇ Br ₂ N ₃ O ₃	542	26.1	96
1596	1668	C ₂₄ H ₃₀ F ₂ N ₄ O ₂	445	22.9	Q
1597	1669	C ₂₄ H ₃₁ FN ₄ O ₂	427	24.0	Q
1598	1670	C ₂₄ H ₃₁ IN ₄ O ₂	535	28.1	Q
1599	1671	C ₂₅ H ₃₁ F ₃ N ₄ O ₃	493	26.8	Q
1600	1672	C ₂₅ H ₃₁ F ₃ N ₄ O ₂	478	24.7	Q
1601	1673	C ₂₄ H ₂₉ BrClN ₃ O ₂	508	24.9	98

Table 29 (continued)

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Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1602	1674	C ₂₀ H ₂₂ Br ₂ FN ₃ O ₃	532	25.6	96
1603	1675	C ₂₂ H ₂₅ F ₃ N ₄ O ₂	435	21.5	99
1604	1676	C ₂₂ H ₂₆ F ₂ N ₄ O ₂	417	21.4	Q
1605	1677	C ₂₂ H ₂₆ BrFN ₄ O ₂	479	23.4	98
1606	1678	C ₂₂ H ₂₆ FIN ₄ O ₂	525	27.4	Q
1607	1679	C ₂₂ H ₂₆ CIFN ₄ O ₂	433	22.4	Q
1608	1680	C ₂₃ H ₂₆ F ₄ N ₄ O ₃	483	25.5	Q
1609	1681	C ₂₃ H ₂₆ F ₄ N ₄ O ₂	467	23.2	99
1610	1682	C ₂₃ H ₂₆ BrCIFN ₃ O	498	24.2	98
1611	1683	C ₂₇ H ₂₈ Br ₂ N ₄ O ₄	633	31.8	Q
.1612	1684	C ₂₉ H ₃₁ F ₂ N ₅ O ₃	536	28.3	Q
1613	1685	C ₂₉ H ₃₂ FN ₅ O ₃	518	31.1	Q
1614	1686	C29H32BrN5O3	578	29.6	Q
1615	1687	C ₂₉ H ₃₂ IN ₅ O ₃	626	32.4	Q
1616	1688	C ₂₉ H ₃₂ CIN ₅ O ₃	534	28.2	Q
1617	1689	C ₃₀ H ₃₂ F ₃ N ₅ O ₄	584	31.7	Q
1618	1690	C ₃₀ H ₃₂ F ₃ N ₅ O ₃	568	30.6	Q
1619	1691	C ₂₉ H ₃₀ BrClN ₄ O ₃	599	31.4	Q
Note:	Q means "Quar	ntitative".			

[0262] For example Compd. Nos. 1245 and 1600 exhibited the following NMR spectra.

[0263] Comps. No. 1245: 1 H NMR (270 MHz, CDCl₃) δ 1.20-1.97 (m, 7H), 2.80-2.86 (m, 2H), 3.19 (t, J = 6.5 Hz, 2H), 3.43 (s, 2H), 4.02 (d, J = 5.3 Hz, 2H), 5.52 (br s, 2H), 6.44 (d, J = 11.9, 6.6 Hz, 1H), 7.02 (br s, 1H), 7.21-7.32 (m, 5H). [0264] Compd. No. 1600: 1 H NMR (270MHz, CDCl₃) δ 1.25-1.97 (m, 9H), 2.82-2.87 (m, 2H), 3.21 (t, J = 6.5 Hz, 2H), 3.44 (s, 2H), 4.06(d, J = 5.1 Hz, 2H), 5.98 (br s, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.87 (br s, 1H), 7.26 (s, 4H), 7.43 (dd, J = 5.9 Hz, 1H), 7.64 (s, 1H).

[Example 1620] Synthesis of 1-(4-chorobenzyl)-4-[[N-(4-isopropylphenylsulfonyl)glycyl]aminomethyl]piperidine (Compd. No. 869)

[0265] A (piperidinomethyl)polystyrene resin (28 mg, 2.8 mmol/g) and 4-isopropylbenzenesulfonyl chloride (1.5 equivalents) were added to a chloroform (2 mL) solution of 1-(4-chlorobenzyl)-4-[(glycylamino)methyl]piperidine (14.8 mg, 0.05 mmol). The resulting mixture was stirred at 25 °C for 16 hours, then filtered and concentrated to thereby afford 1-(4-chlorobenzyl)-4-[[N-(4-isopropylphenylsulfonyl)glycyl]aminomethyl]piperidine (Compd. No. 869) (22.1 mg, 92%). The purity was determined by RPLC/MS (86%). ESI/MS m/e 478 (M++H, C₂₄H₃₂N₃O₃S).

[Examples 1621 to 1627]

[0266] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1620. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 30.

Table 30

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Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1621	865	C ₂₂ H ₂₈ CIN ₃ O ₃ S	450	16.2	72

Table 30 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1622	866	C ₂₂ H ₂₅ CIF ₃ N ₃ O ₃ S	504	8.8	35
1623	867	C ₂₃ H ₂₄ CIF ₆ N ₃ O ₃ S	572	8.0	28
1624	868	C ₂₃ H ₃₀ ClN ₃ O ₃ S	464	9.6	41
1625	870	C ₂₂ H ₂₈ CIN ₃ O ₃ S	450	8.8	39
1626	871	C ₂₅ H ₃₄ ClN ₃ O ₃ S	492	11.1	45
1627	872	C ₂₁ H ₂₆ CIN ₃ O ₃ S	436	9.6	44

[Example 1628] Synthesis of 1-(4-chlorobenzyl-4-[[2-(3-(4-trifluoromethylphenyl)ureido)acetylamino]methyl]piperidine (Compd. No. 852)

[0267] A (piperidinomethyl)polystyrene resin (28 mg, 2.8 mmol/g) and 3-(trifluoromethyl)phenyl isocyanate (1.3 equivalents) were added to a chloroform (2 mL) solution of 1-(4-chlorobenzyl)-4-[(glycylamino)methyl]piperidine (14.8 mg, 0.05 mmol). The resulting mixture was stirred at 25 °C for 16 hours, and an (aminomethyl)polystyrene resin was added to the obtained mixture. The resulting mixture was stirred at 25 °C for 16 hours to trap the remaining isocyanate. The obtained mixture was filtered and concentrated to thereby provide 1-(4-chlorobenzyl)-4-[[2-(3-(4-trifluoromethyl)phenyl)ureido)acetylamino]methyl]piperidine (Compd. No. 852) (19 mg, 78%). The purity was determined by RPLC/MS (92%). ESI/MS m/e 483 (M*+H, C₂₃H₂₆CIF₃N₄O₂).

[Examples 1629 to 1641]

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[0268] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1628. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 31.

Table 31

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)	
1629	851	C ₂₃ H ₂₆ CIF ₃ N ₄ O ₂	483	13.2	55	
1630	853	C ₂₂ H ₂₇ CIN ₄ O ₂	416	8.5*	32	
1631	854	C ₂₃ H ₂₉ CIN ₄ O ₂	429	11.4*	42	
1632	855	C ₂₃ H ₂₉ CIN ₄ O ₂	429	10.1*	37	
1633	856	C ₂₄ H ₂₉ CIN ₄ O ₃	457	10.3*	36	
1634	857	C ₂₃ H ₂₉ CIN ₄ O ₃	445	10.9*	39	
1635	858	C ₂₃ H ₂₉ CIN ₄ O ₃	445	8.6*	31	
1636	859	C ₂₂ H ₂₆ Cl ₂ N ₄ O ₂	449	11.0*	39	
1637	860	C ₂₃ H ₂₆ CIN ₅ O ₂	440	9.2*	33	
1638	861	C ₂₂ H ₂₇ CIN₄OS	431	13.3	62	
1639	862	C ₂₃ H ₂₉ CIN ₄ OS	445	15.3	69	
1640	863	C ₂₃ H ₂₉ CIN ₄ O ₂ S	461	14.7	64	
1641	864	C ₂₃ H ₂₉ CIN ₄ O ₂ S	461	13:1	57	
Note:	Note: * indicates "yield (mg) of trifluoroacetate".					

[Example 1642] Synthesis of 1-(4-chlorobenzyl)-4-[[N-(3-ethoxybenzoyl)-D-phenylalanyl]aminomethyl]piperidine (Compd. No. 2091)

[0269] Triethylamine (0.090 mL), N-(tert-butoxycarbonyl)-D-(phenylalanine) (122 mg), EDCI (89 mg) and HOBt (62 mg) were added to a chloroform (3 mL) solution of 1-(4-chlorobenzyl)-4-(aminomethyl)piperidine (100 mg). The result-

ing mixture was stirred at room temperature for 17 hours, and the reaction mixture was washed with a 1 M aqueous solution of NaOH (2 mL \times 2) and brine (2 mL). The organic layer was dried and concentrated to thereby afford 1-(4-chlorobenzyl)-4-[[N-(tert-butoxycarbonyl)-D-phenylalanyl]aminomethyl]piperidine.

[0270] The resulting 1-(4-chlorobenzyl)-4-[[N-(tert-butoxycarbonyl)-D-phenylalanyl]aminomethyl]piperidine was dissolved in methanol (5 mL), and a 4 M dioxane solution of HCl was then added to the solution. The obtained solution was stirred at room temperature for 19 hours and concentrated.

[0271] Triethylamine (0.090 mL), EDCI (90 mg) and HOBt (68 mg) were added to a chloroform solution (1 mL) of the obtained residue and 3-ethoxybenzoic acid (80 mg, 0.48 mmol). The resulting mixture was stirred at room temperature for 17 hours. The resulting reaction mixture was washed with a 1 M aqueous solution of NaOH (1.5 mL×2) and brine (1.5 mL). The organic layer was dried, concentrated and purified by column chromatography (SiO₂, dichloromethane/methanol = 95:5) to provide 1-(4-chlorobenzyl)-4-[[N-(3-ethoxybenzoyl)-D-phenylalanyl]aminomethyl]piperidine (Compd. No. 2091) (183.5 mg, 82%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 534.0 (M++H, $C_{31}H_{36}CIN_3O_3$).

[Examples 1643 to 1657]

[0272] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of 1642. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 32.

Table 32

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1643	2092	C ₃₃ H ₃₇ CIN ₄ O ₃	572.8	152.9	64
1644	2093	C ₂₇ H ₃₆ CIN ₃ O ₃ S	518.0	177.4	82
1645	2094	C ₂₉ H ₃₄ CIN ₃ O ₃ S	539.9	164.4	73
1646	2095	C ₂₈ H ₃₈ CIN ₃ O ₃	500.0	139.1	66
1647	2096	C ₃₁ H ₄₂ CIN ₃ O ₃	540.0	161.7	71
1648	2097	C ₂₇ H ₃₆ CIN ₃ O ₃	485.8	157.8	78
1649	2098	C ₃₁ H ₃₅ Cl ₂ N ₃ O ₃	567.9	172.2	72
1650	2099	C ₃₀ H ₃₄ CIN ₃ O ₃	519.8	144.7	66
1651	2100	C ₃₂ H ₃₈ CIN ₃ O ₄	564.0	181.5	77
1652	2101	C ₃₈ H ₄₂ CIN ₃ O ₄	639.9	192.3	72
1653	2103	C ₃₃ H ₄₀ CIN ₃ O ₄	577,8	159.9	66
1654	2104	C ₂₈ H ₃₆ CIN ₃ O ₅	530.1	99.7	45
1655	2115	C ₂₇ H ₃₆ CIN ₃ O ₃	486.2	122.9	60
1656	2116	C ₂₈ H ₃₈ CIN ₃ O ₃	500.1	118.3	57
1657	2117	C ₂₈ H ₃₄ CIN ₅ O ₃	524.1	98.3	45

[Reference Example 29] Synthesis of 1-(tert-butoxycarbonyl)-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl] piperidine

[0273] N-[3-(Trifluoromethyl)benzoyl]glycine (4.22 g, 17.0 mmol), EDCI (4.25 g, 22.1 mmol), 1-hydroxybenzotriazole hydrate (2.99 g, 22.1 mmol) and triethylamine (1.72 g) were added to an anhydrous dichloromethane (200 mL) solution of 1-(tert-butoxycarbonyl)-4-(aminomethyl)piperidine (4.03 g). The resulting reaction mixture was stirred at 25 °C for 20 hours, and H_2O (100 mL) was then added to the mixture. The obtained mixture was extracted with dichloromethane (50 mL \times 2). The extracts were combined, washed with H_2O (50 mL \times 2) and brine (50 mL), dried (over MgSO₄) and concentrated to thereby afford a yellow oil. The obtained crude product was purified by column chromatography (SiO₂, 70% ethyl acetate-hexane) to provide 1-(tert-butoxycarbonyl)-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl] piperidine as a white solid (6.39 g, 85%). ¹H NMR(CDCl₃, 300MHz) δ 1.4 (s, 9H), 1.0-1.8 (m, 5H), 2.6-2.8 (m, 2H), 3.15-3.3 (m, 2H), 4.0-4.3 (m, 4H), 6.6-6.7 (m, 1H), 7.64 (s, 1H), 7.60 (dd, 1H, J = 7.2, 7.2 Hz), 7.79 (d, 1H, J = 7.2 Hz), 8.0 (d, 1H, J = 7.2 Hz), 8.11 (s, 1H). The purity was determined by RPLC/MS (97%). ESI/MS m/e 444.3 (M++H,

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C₂₁H₂₈N₃O₄).

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[Reference Example 30] Synthesis of 4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine

[0274] A 1 M HCl-Et₂O (55 mL) was added to a methanol (40 mL) solution of 1-(tert- butoxycarbonyl)-4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (2.29 g, 5.16 mmol). The obtained mixture was stirred at 25 °C for 15 hours, and the solvent was removed under reduced pressure. A 2 M aqueous solution of NaOH (100 mL) was added to the mixture, and the resulting mixture was extracted with ethyl acetate (100 mL× 3). The extracts were combined, washed with brine (50 mL), dried (over K₂CO₃) and concentrated to thereby afford a white solid. The obtained crude solid was purified by column chromatography (SiO₂, methanol/dichloromethane/triethylamine = 7:6:1) to provide 4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine as a white solid (1.27 g, 72%). The purity was determined by RPLC/MS (98%). ESI/MS m/e 344.1 (M++H, C₁₆H₂₀N₃O₂).

[Example 1658] Synthesis of 1-[3-(trifluoromethoxy)benzyl]-4-[(N-(3-(trifluoromethyl)benzoyl)glycyl)aminomethyl] piperidine (Compd. No. 927)

[0275] An acetonitrile (1.0 mL) solution of 4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (19.9 mg, 0.058 mmol) and a (piperidinomethyl)polystyrene (55 mg, 2.7 mmol base/g resin) were added to an acetonitrile (1.0 mL) solution of 3-(trifluoromethoxy)benzyl bromide (12.3 mg, 0.048 mmol). The obtained mixture was stirred at 60 °C for 2.5 hours. Phenyl isocyanate (6.9 mg, 0.048 mmol) was added to the cooled reaction mixture, and the resulting mixture was stirred at 25°C for 1 hour. The reaction mixture was loaded onto a VarianTM SCX column and washed with methanol (20 mL). The product was eluted with a 2 M methanol solution of NH₃ and concentrated to provide 1-[3-(trifluoromethoxy)benzyl]-4-[(N-(3-(trifluoromethyl)benzoyl)glycyl)aminomethyl]piperidine (Compd. No. 927) as an off-white oil (22.8 mg, 91%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 518.1 (M++H, C₂₄H₂₅F₆N₃O₃).

[Examples 1659 to 1710]

[0276] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1658. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 33.

Table 33

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1659	875	C ₂₃ H ₂₆ F ₃ N ₃ O ₂	434	6.3	40
1660	876	C ₂₃ H ₂₅ BrF ₃ N ₃ O ₂	512	4.3	23
1661	877	C ₂₄ H ₂₅ F ₃ N ₄ O ₂	459	11.3	68
1662	878	C ₂₃ H ₂₅ F ₃ N ₄ O ₄	479	8.3	48
1663	884	C ₂₅ H ₂₉ F ₃ N ₄ O ₃	491	10.8	61
1664	885	C ₂₄ H ₂₈ F ₃ N ₃ O ₄ S	512	9.0	49
1665	886	C ₂₃ H ₂₅ F ₄ N ₃ O ₂	452	12.7	78
1666	887	C ₂₄ H ₂₅ F ₆ N ₃ O ₂	502	13.9	77
1667	888	C ₂₃ H ₂₆ F ₃ N ₃ O ₃	450	11.5	71
1668	889 -	C ₂₉ H ₃₀ F ₃ N ₃ O ₂	510	12.4	68
1669	890	C ₂₇ H ₂₈ F ₃ N ₃ O ₂	484	12.0	69
1670	891	C ₂₃ H ₂₄ Cl ₂ F ₃ N ₃ O ₂	502	11.4	63
1671	892	C ₂₄ H ₂₈ F ₃ N ₃ O ₃	464	11.7	70
1672	893	C ₂₄ H ₂₆ F ₃ N ₅ O ₅	522	13.9	74
1673	894	C ₂₆ H ₃₂ F ₃ N ₃ O ₃	492	11.3	64
1674	895	C ₂₄ H ₂₈ F ₃ N ₃ O ₂	448	4.8	30

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Table 33 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1675	896	C ₂₄ H ₂₅ F ₃ N ₄ O ₂	459	17.5	q
1676	897	C ₂₄ H ₂₆ F ₃ N ₃ O ₄	478	9.2	57
1677	898	C ₂₄ H ₂₆ F ₃ N ₃ O ₄	478	8.9	55
1678	899	C ₂₄ H ₂₈ F ₃ N ₃ O ₃	464	13.7	82
1679	900	C ₂₅ H ₂₈ F ₃ N ₃ O ₄	492	18.6	Q
1680	901	C ₂₉ H ₃₀ F ₃ N ₃ O ₂	510	13.7	75
1681	902	C ₂₃ H ₂₄ F ₃ N ₅ O ₆	524	12.6	67
1682	903	C ₂₅ H ₃₀ F ₃ N ₃ O ₄	494	14.0	79
1683	906	C ₂₅ H ₃₀ F ₃ N ₃ O ₂	462	11.2	67
1684	907	C ₃₁ H ₃₄ F ₃ N ₃ O ₂	538	19.6	75
1685	908	C ₃₀ H ₃₁ F ₃ N ₄ O ₃	553	30.4	76
1686	909	C ₃₀ H ₃₁ F ₃ N ₄ O ₃	553	12.6	63
1687	910	C ₂₃ H ₂₄ Cl ₂ F ₃ N ₃ O ₂	502	11.0	61
1688	911	C ₂₃ H ₂₅ CIF ₃ N ₃ O ₂	468	20.2	89
1689	912	C ₂₃ H ₂₄ Br ₂ F ₃ N ₃ O ₂	590	20.2	95
1690	913	C ₂₄ H ₂₈ F ₃ N ₃ O ₃	464	12.6	76
1691	914	C ₃₀ H ₃₂ F ₃ N ₃ O ₃	540	13.9	72
1692	915	C ₂₄ H ₂₈ F ₃ N ₃ O ₃	464	8.3	25
1693	916	C ₂₂ H ₂₅ F ₃ N ₄ O ₂	435	2.5	8
1694	917	C ₂₂ H ₂₅ F ₃ N ₄ O ₂	435	2.7	9
1695	918	C ₂₆ H ₃₀ F ₃ N ₃ O ₄	506	3.9	22
1696	919	C ₂₄ H ₂₈ F ₃ N ₃ O ₂	448	15.9	99
1697	920	C ₂₄ H ₂₅ F ₆ N ₃ O ₃	518	20.3	81
1698	921	C ₂₇ H ₂₈ F ₃ N ₃ O ₂	484	15.5	89
1699	922	C ₂₀ H ₂₆ F ₃ N ₃ O ₂	398	7.3	51
1700	923	C ₂₉ H ₂₉ CIF ₃ N ₃ O ₂	544	12.5	48
1701	928	C ₂₄ H ₂₅ F ₆ N ₃ O ₃	518	21.4	86
1702	929	C ₂₄ H ₂₈ F ₃ N ₃ O ₂ S	480	23.7	Q
1703	930	C24H28F3N302	448	21.3	99
1704	931	C ₂₄ H ₂₅ F ₃ N ₄ O ₂	459	21.4	97
1705	932	C ₂₃ H ₂₄ CIF ₃ N ₄ O ₄	513	15.6	63
1706	933	C ₂₄ H ₂₈ F ₃ N ₃ O ₂	448	16.6	77
1707	934	C ₂₂ H ₂₅ F ₃ N ₄ O ₂	435	18.0	43
1708	935	C ₂₃ H ₂₅ F ₃ N ₄ O ₄	479	15.1	65
1709	936	C ₂₃ H ₂₅ F ₃ N ₄ O ₄	479	15.4	67
1710	1615	C ₂₄ H ₂₅ F ₆ N ₃ O ₂ S	534.2	26.3	99

[Example 1711] Synthesis of 1-[4-(dimethylamino)benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl] piperidine (Compd. No. 937)

[0277] A methanol (1.0 mL) solution of 4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (20.0 mg, 0.058 mmol) and NaBH₃CN (16.5 mg) were added to a 5% acetic acid solution (1.0 mL) of 4-(dimethylamino)benzal-dehyde (30.4 mg, 0.204 mmol), and the resulting mixture was stirred at 60 °C for 19 hours. The solvent was evaporated to provide a solid. Acetonitrile (2.0 mL) and phenyl isocyanate (6.9 mg, 0.048 mmol) were added to the solid, and resulting mixture was stirred at 25 °C for 1 hour. The reaction mixture was loaded onto a Varian™ SCX column and washed with methanol (20 mL). The obtained crude product was eluted with a 2 M NH₃-methanol (6 mL), and the eluate was concentrated to thereby afford 1-[4-(dimethylamino)benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 937) as an off-white oil (13.5 mg, 49%). The purity was determined by RPLC/MS (87%). ESI/MS m/e 477.3 (M++H, C₂₅H₃₁F₃N₄O₂).

[Examples 1712 to 1729]

[0278] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to Example 1711. The obtained products, if necessary, were purified by preparative TLC (SiO₂) to provide the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 34.

Table 34

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Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)		
1712	879	C ₂₄ H ₂₆ F ₃ N ₃ O ₄	478	13.0	. 62		
1713	880	C ₂₄ H ₂₆ F ₃ N ₃ O ₄	478	16.3	78		
1714	881	C ₂₃ H ₂₅ BrF ₃ N ₃ O ₂	512	11.4	51		
1715	882	$C_{29}H_{30}F_3N_3O_3$	526	13.4	58		
1716	883	C ₂₃ H ₂₅ CIF ₃ N ₃ O ₂	468	7.9	39		
1717	904	$C_{23}H_{26}F_3N_3O_3$	450	3.3	17		
1718	905	C ₂₁ H ₂₃ F ₃ N ₄ O ₄ S	485	27.7	98		
1719	938	C ₂₃ H ₂₄ CIF ₄ N ₃ O ₂	486	8.6	30		
1720	939	C ₂₃ H ₂₄ CIF ₃ N ₄ O ₄	513	11.0	37		
1721	940	C ₂₃ H ₂₆ F ₃ N ₃ O ₃	450	5.5	21		
1722	941	C ₂₄ H ₂₄ CIF ₆ N ₃ O ₂	536	11.2	36		
1723	987	C ₃₀ H ₃₂ F ₃ N ₃ O ₂	524	17.5	76		
1724	1449	C ₂₅ H ₃₀ F ₃ N ₃ O ₂	. 462	21.6	80		
1725	1450	C ₂₆ H ₃₂ F ₃ N ₃ O ₂	476	23.5	85		
1726	1452	C ₂₇ H ₃₅ F ₃ N ₄ O ₂	505	5.1	17		
1727	1453	C ₂₆ H ₃₂ F ₃ N ₃ O ₃	492	22.0	77		
1728	1454	C ₂₅ H ₃₀ F ₃ N ₃ O ₃	478	21.4	77		
1729	1456	C ₂₅ H ₂₈ F ₃ N ₃ O ₄	492	23.8	83		

[Example 1730] Synthesis of 1-[3-hydroxy-4-methoxybenzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl] piperidine (Compd. No.1452)

[0279] A 5% acetic acid/methanol (1.0 mL) solution of 4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (20.0 mg, 0.058 mmol) and 3-hydroxy-4-methoxybenzaldehyde (33 mg) was added to a 5% acetic acid/methanol (1.0 mL) solution of NaBH₃CN (16.5 mg), and the, mixture was stirred at 60 °C for 15 hours. The resulting reaction mixture was then loaded onto a Varian™ SCX column and washed with methanol (15 mL). The obtained crude product was eluted with a 2 M NH₃-methanol (5 mL) and concentrated to thereby afford 1-[3-hydroxy-4-methoxybenzyl]-

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4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 1452) (25.8 mg, 92%). The purity was determined by RPLC/MS (91%). ESI/MS m/e 480 (M $^+$ +H, C₂₄H₂₈F₃N₃O₄).

[Examples 1731 to 1733]

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[0280] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1730. The obtained products, if necessary, were purified by preparative TLC to provide the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 35.

Table 35

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1731	1455	$C_{24}H_{28}F_3N_3O_4$	480	24.0	86
1732	1647	C ₂₇ H ₃₄ F ₃ N ₃ O ₂	490.2	23.6	96
1733	1649	C ₂₆ H ₃₂ F ₃ N ₃ O ₂	476.2	23.1	97

[Example 1734] Synthesis of 1-(4-benzylbenzyl)-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 926)

[0281] A chloroform (1.0 mL) solution of methanesulfonyl chloride (4.2 mg, 0.037 mmol) and a (piperidinomethyl) polystyrene (54 mg, 2.7 mmol base/g resin) were added to a chloroform (1.0 mL) solution of 4-(benzyl)benzyl alcohol (8.7 mg, 0.044 mmol), and the resulting mixture was stirred at 25°C for 15 hours. 4-[[N-(3-(Trifluoromethyl)benzoyl) glycyl]aminomethyl]piperidine (15.1mg, 0.044 mmol) and KI (2 mg) were then added to the reaction mixture, and the resulting mixture solution was further stirred at 65 °C for 5 hours. Phenyl isocyanate (5.2 mg) was added to the cooled reaction mixture, and the obtained mixture was stirred at 25 °C for 1 hour. The resulting reaction mixture was loaded onto a VarianTM SCX column and washed with methanol (20 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated to thereby afford 1-(4-benzylbenzyl)-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 926) as an off-white oil (5.6 mg, 29%). The purity was determined by RPLC/MS (94%). ESI/MS m/e 524.1 (M++H, C₃₀H₃₂F₃N₃O₂).

[Reference Example 31] Synthesis of 4-[[(N-(benzyloxycarbonyl)glycyl)amino]methyl]-1-(tert-butoxycarbonyl) piperidine

[0282] Triethylamine (2.8 mL, 20 mmol), N-(benzyloxycarbonyl)glycine (3.77 g, 18 mmol), EDCI (3.45 g, 18 mmol) and HOBt (2.43 g, 18 mmol) were added to a chloroform (80 mL) solution of 4-(aminomethyl)-1-(tert-butoxycarbonyl) piperidine (3.54 g, 16.5 mmol). The resulting mixture was stirred at room temperature for 15 hours, and a 2 M aqueous solution of NaOH (100 mL) was then added to the mixture. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (100 mL× 3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography (SiO₂, ethyl acetate) to provide 4-[[(N-(benzyloxycarbonyl)glycyl)amino]methyl]-1-(tert-butoxycarbonyl)piperidine as an amorphous solid (6.27 g, 94%).

[Reference Example 32] Synthesis of 4 [(glycylamino)methyl]-1-(tert-butoxycarbonyl)piperidine

[0283] A methanol (100 mL) solution of 4-[[(N-(benzyloxycarbonyl)glycyl)amino]methyl]-1-(tert-butoxycarbonyl)piperidine (6.26 g, 15.4 mmol) was hydrogenated in the presence of a 5% palladium carbon (620 mg) at room temperature for 7 hours. The catalyst was removed by filtration through Celite, and the filtrate was then concentrated to thereby afford 4-[(glycylamino)methyl)-1-(tert- butoxycarbonyl)piperidine as a solid (3.84 g, 92%).

[Reference Example 33] Synthesis of 4-[[(N-(2-amino-5-chlorobenzoyl)glycyl)amino]methyl]-1-(tert-butoxycarbonyl) piperidine

[0284] Triethylamine (0.75 mL, 5.4 mmol), 2-amino-5-chlorobenzoic acid (840 mg, 4.9 mmol), EDCI (940 mg, 4.9 mmol) and HOBt (660 mg, 4.9 mmol) were added to a chloroform (25 mL) solution of 4-[(glycylamino)methyl]-1-(tert-butoxycarbonyl)piperidine (1.33 g, 4.90 mmol). The resulting mixture was stirred at room temperature for 3 hours, and a 2 M aqueous solution of NaOH (20 mL) was then added to the mixture. The organic layer was separated, and the

aqueous layer was extracted with dichloromethane (20 mL \times 3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography (SiO₂, ethyl acetate) to thereby provide 4-[[(N-(2-amino-5-chlorobenzoyl)glycyl)amino]methyl]-1-(tert-butoxycarbonyl) piperidine as a solid (1.63 g, 78%).

[Reference Example 34] Synthesis of 4-[[(N-(2-amino-5-chlorobenzoyl)glycyl)amino]methyl]piperidine

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[0285] A 4 M dioxane solution of HCI (9.5 mL) was added to a methanol (20 mL) solution of 4-[[(N-(2-amino-5-chlorobenzoyl)glycyl)amino]methyl]-1-(tert-butoxycarbonyl)piperidine (1.63 g, 3.84 mmol), and the resulting mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated, and a 2 M aqueous solution of NaOH (20 mL) was added to the resulting residue. The obtained mixture was extracted with dichloromethane (20 mL \times 3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to thereby afford 4-[[(N-(2-amino-5-chlorobenzoyl)glycyl)amino]methyl]piperidine (1.19 g, 95%). ¹H NMR (CDCl₃, 270MHz). δ 1.10-1.76 (m, 4H), 2.55 (td, J = 2.4 and 12.2 Hz, 2H), 3.00-3.10 (m, 2H), 3.17 (t, J = 6.2 Hz, 2H), 3.48 (s, 2H), 4.03 (d, J = 4.9 Hz, 2H), 5.50 (br. s, 2H), 6.11-6.23 (m, 1H), 6.60 (d. J = 8.8 Hz, 1H), 6.85-7.02 (m, 1H), 7.15 (dd, J = 2.7and 8.8 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H). ESI/MS m/e 325.2 (M++H, C₁₅H₂₃ClN₄O₂).

[0286] Further, 4-[[(N-(2-amino-5-bromobenzoyl)glycyl)amino]methyl]piperidine was synthesized by using the corresponding starting material and reactants according to Reference Examples 33 and 34. 951 mg, 64% (two steps); ESI/MS m/e 369.2 (M++H, $C_{15}H_{21}BrN_4O_2$).

[Example 1735] Synthesis of 4-[[(N-(2-(tert-butoxycarbonylamino)-4, 5-difluorobenzoyl)glycyl)amino]methyl]-1-(4-chlorobenzyl)piperidine

[0287] Triethylamine (1.1 mL, 8 mmol), 2-(tert-butoxycarbonylamino)-4,5-difluorobenzoic acid (607 mg, 2.2 mmol), EDCI (422 mg, 2.2 mmol) and HOBt (337 mg, 2.2 mmol) were added to a dichloromethane (20 mL) solution of 1-(4-chlorobenzyl)-4-[(glycylamino)methyl]piperidine dihydrochloride (738 mg, 2 mmol), and the resulting mixture was stirred at room temperature for 14 hours. A 0.6 M aqueous solution of NaOH (50 mL) was then added to the mixture, and the obtained mixture was extracted with dichloromethane (3 times). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to thereby provide 4-[[(N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzyl)glycyl)amino]methyl]-1-(4-chlorobenzyl)piperidine (1.01 g, 92%). ESI/MS m/e 551.3 (M++H, $C_{27}H_{33}CIF_2N_4O_4$).

[0288] Moreover, 4-[[(N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl)amino]methyl]-1-(4 chlorobenzyl)piperidine was synthesized by using the corresponding starting material and reactants according to the above method. 3.03 g, 82%; ESI/MS m/e 583.2 (M++H, $C_{28}H_{34}CIF_3N_4O_4$).

[Reference Example 35] Synthesis of 4-[[(N-(2-amino-5-trifluoromethylbenzoyl)glycyl)amino]methyl]piperidine

[0289] A 5% formic acid/methanol solution (10 mL) of 1-(4-chlorobenzyl)-4-[[(N-(2-amino-5-trifluoromethylbenzoyl) glycyl)amino]methyl]piperidine (447 mg, 0.93 mmol) and $Pd(OH)_2$ (60 mg, 0.23 mmol) was stirred at 50 °C for 14 hours. The palladium catalyst was removed by filtration through Celite, and the filtrate was concentrated. A 1 M aqueous solution of NaOH (15 mL) was added to the resulting residue, and the obtained mixture was extracted with ethyl acetate (30 mL×3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography (SiO₂ ethyl acetate/methanol/triethylamine = 70:25: 5) to thereby afford 4-[[(N-(2-amino-5-trifluoromethylbenzoyl)glycyl)amino]methyl]piperdine (284mg, 86%). ESI/MS m/ e 359.0 (M++H, $C_{16}H_{21}F_3N_4O_2$).

[0290] Furthermore, 4-[[(N-(2-amino-4,5-difluorobenzoyl)glycyl)amino]methyl]piperidine, 4-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethoxybenzoyl)glycyl]aminomethyl]piperidine and 4-[[(N-(2-(tert-butoxycarbonylamino)-5-trifluoromethoxybenzoyl)glycyl)amino]methyl]piperidine were synthesized by using the respective corresponding starting materials and reactants according to the above method.

[0291] 4-[[(N-(2-amino-4,5-difluorobenzoyl)glycyl)amino]methyl]piperidine: 564 mg, 89%; ESI/MS m/e 327.2 (M⁺+H, $C_{15}H_{20}F_2N_4O_2$).

[0292] 4-[[(N-(2-(tert-butoxycarbonylamino)-5-trifluoromethoxybenzoyl)glycyl)amino]methyl]piperidine: quantitative; 1 H NMR (CDCl₃, 400MHz) δ 1.10-1.25 (m, 2H), 1.45-1.73 (m, 3H), 1.51 (s, 9H), 2.53-2.64 (m, 2H), 3.04-3.13 (m, 2H), 3.22 (t, J = 6.3 Hz, 2H), 4.09 (d, J = 4.6 Hz, 2H), 5.91 (br. s, 1H), 7.08 (br, s., 1H), 7.32 (d. J = 9.0 Hz, 1H), 7.38 (s, 1H), 8.43 (d, J = 9.0 Hz, 1H).

[0293] 4-[[(N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl)amino]methyl]piperidine: 310 mg, 40%; ESI/ MS m/e 427.3 (M++H, $C_{20}H_{28}F_2N_4O_4$).

[0294] 4-[[(N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl)amino]methyl]piperidine: 1.35 g, 57%;

ESI/MS m/e 459.3 (M++H, C₂₁H₂₉F₃N₄O₄).

[Example 1736] Synthesis of 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]aminomethyl]-1-(4-ethoxybenzyl)piperidine (Compd. No. 1429) and 1-(4-ethoxybenzyl)-4-[[N-(2-(4-ethoxybenzyl)amino-5-chlorobenzoyl)glycyl]aminomethyl] piperidine (Compd. No. 1433)

[0295] A methanol (0.4 mL) solution of sodium cyanoborolfydride (140 mmol) was added to a mixture of 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]aminomethyl]piperidine (0.10 mmol) with 4-ethoxybenzaldehyde (0.10 mmol); acetic acid (0.050 mL) and methanol (1.6 mL), and the resulting mixture was stirred at 60 °C for 14 hours. The obtained reaction mixture was loaded onto a VarianTM SCX column and washed with methanol (20 mL). The resulting products were eluted with a 2 M methanol solution of NH₃, concentrated and purified by preparative TLC (SiO₂, ethyl acetate/methanol) to thereby provide 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]aminomethyl]-1-(4-ethoxybenzyl)piperidine (Compd. No. 1429) and 1-(4-ethoxybenzyl)-4-[[N-(2-(4-ethoxybenzylamino-5-chlorobenzoyl)glycyl]aminomethyl]piperidine (Compd. No. 1433).

[0296] Compd. No. 1429: 4.5 mg, 20%. The purity was determined by RPLC/MS (95%). ESI/MS m/e 459.2 (M++H, $C_{24}H_{31}CIN_4O_3$).

[0297] Compd. No. 1433: 8.4 mg, 28%. The purity was determined by RPLC/MS (98%). ESI/MS m/e 593.2 (M++H, $C_{33}H_{41}CIN_4O_4$).

20 [Examples 1737 to 1779]

[0298] The compounds used in the present invention were synthesized by using respective starting materials and reactants according to the method of Example 1736. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 36.

Table 36

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1737	1430	C ₂₄ H ₂₉ CIN ₄ O ₄	473.0	3.1	13
1738	1431	C ₂₄ H ₃₁ BrN ₄ O ₃	505.2	5.8	23
1739	1432	C ₂₄ H ₂₉ BrN ₄ O ₄	517.0	4.1	'16
1740	1434	C ₃₃ H ₄₁ BrN ₄ O ₆	637.2	9.7	30
1741	1435	C ₂₄ H ₃₁ CIN ₄ O ₂	443.2	9.7	44
1742	1436	C ₂₅ H ₃₃ CIN ₄ O ₂	457.2	12.5	55
1743	1437	C ₂₅ H ₃₃ CIN ₄ O ₃	473.2	9.4	40
1744	1438	C ₂₄ H ₃₁ BrN ₄ O ₂	489.2	5.9	24
1745	1439	C ₂₅ H ₃₃ BrN ₄ O ₂	503.2	15.2	61
1746	1440	C ₂₅ H ₃₃ BrN ₄ O ₃	519.2	11.0	43
1747	1441	C ₂₃ H ₂₉ BrN ₄ O ₂ S	507.2	9.3	37
1748	1442	C ₃₃ H ₄₁ CIN ₄ O ₂	561.4	6.8	24
1749	1443	C ₃₅ H ₄₅ CIN ₄ O ₂	589.4	9.8	33
1750	1444	C ₃₅ H ₄₅ CIN ₄ O ₄	621.4	9.4	30
1751	1445	C ₃₃ H ₄₁ BrN ₄ O ₂	605.2	6.5	21
1752	1446	C ₃₅ H ₄₅ BrN ₄ O ₂	635.2	10.7	34
1753	1447	C ₃₅ H ₄₅ BrN ₄ O ₄	665.4	12.4	37
1754	1448	C ₃₁ H ₃₇ BrN ₄ O ₂ S ₂	643.2	7.6	24
1755	1457	C ₂₄ H ₃₂ CIN ₅ O ₂	458.2	4.5	20
1756	1458	C ₂₃ H ₂₉ CIN ₄ O ₄	461.2	6.0	26
1757	1459	C ₂₄ H ₃₂ BrN ₅ O ₂	504.0	6.8	27

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Table 36 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1758	1460	C ₂₃ H ₂₉ BrN ₄ O ₄	505.0	8.0	32
1759	1461	C ₃₁ H ₃₇ CIN ₄ O ₆	597.2	5.9	20
1760	1462	C ₃₁ H ₃₇ BrN ₄ O ₆	643.2	6.0	19
1761	1514	C ₂₆ H ₃₆ CIN ₅ O ₂	486.2	5.5	23
1762	1515	C ₂₃ H ₂₉ CIN ₄ O ₄	463.0	5.8	25
1763	1516	C ₂₆ H ₃₆ BrN ₅ O ₂	530.2	4.2	16
1764	1517	C ₂₃ H ₂₉ BrN ₄ O ₄	505.0	6.5	26
1765	1518	C ₃₁ H ₃₇ CIN ₄ O ₆	597.2	4.3	14
1766	1519	C ₃₁ H ₃₇ BrN ₄ O ₆	641.2	5.3	17
1767	1570	C ₂₃ H ₂₉ CIN ₄ O ₂ S	461.0	2.7	12
1768	1571	C ₃₁ H ₃₇ CIN ₄ O ₂ S ₂	597.2	4.9	16
1769	1651	C ₃₇ H ₄₉ BrN ₄ O ₂	663.2	5.5	17
1770	1652	C ₂₆ H ₃₅ BrN ₄ O ₂	515.2	6.0	23
1771	1653	C ₃₅ H ₄₅ BrN ₄ O ₂	633.2	5.0	16
1772	1654	C ₂₅ H ₃₃ BrN ₄ O ₂	501.0	6.2	25
1773	1655	C ₃₇ H ₄₉ CIN ₄ O ₂	617.4	5.6	18
1774	1656	C ₂₆ H ₃₅ CIN ₄ O ₂	471.2	5.9	25
1775	1657	C ₃₅ H ₄₅ CIN ₄ O ₂	589.2	4.6	16
1776	1658	C ₂₅ H ₃₃ CIN ₄ O ₂	457.2	5.3	23
1777	1785	C ₂₆ H ₃₃ F ₃ N ₄ O ₂	491.2	4.7	12.8
1778	1786	C ₂₅ H ₂₉ F ₃ N ₄ O ₃	491.2	3.7	10.1
1779	1804	C ₂₅ H ₃₂ F ₂ N ₄ O ₂	459.2	3.3	9.6

[Example 1780] Synthesis of 4-[[N-(2-amino-5-trifluoromethoxybenzoyl)glycyl]aminomethyl]-1-(4-isopropylbenzyl) piperidine (Compd. No. 1903)

[0299] Acetic acid (10 mL) was added to a mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-5-(trifluoromethoxy)ben-zoyl)glycyl]aminomethyl]piperidine (0.050 mmol) with 4-isopropylbenzaldehyde (0.060 mmol), NaH₃CN (0.15 mmol) and methanol (1.3 mL), and the resulting mixture was stirred at 60 °C for 8 hours, cooled to room temperature, then loaded onto a VarianTM SCX column and washed with methanol (10 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. A 4 M dioxane solution of HCl (2 mL) was then added to the resulting residue, and the obtained solution was stirred at room temperature overnight, concentrated and then purified by preparative TLC to provide 4-[[N-(2-amino-5-trifluoromethoxybenzoyl)glycyl]aminomethyl]-1-(4-isopropylbenzyl) piperidine (Compd. No. 1903) (6.6 mg, 26%). The purity was determined by RPLC/MS (93%). ESI/MS m/e 507 (M++H, C₂₆H₃₃F₃N₄O₃).

[Examples 1781 to 1783]

[0300] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1780. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 37.

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Table 37

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1781	1904	C ₂₆ H ₃₃ F ₃ N ₄ O ₃	507	9.6	37.9
1782	1917	C ₂₅ H ₃₁ F ₃ N ₄ O ₅	525.2	1.2	3.1
1783	1918	C ₂₄ H ₂₉ F ₃ N ₄ O ₄	495.2	2.8	7.5

[Example 1784] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(5-bromo-2-ethoxybenzyl) piperidine (Compd. No. 2052)

[0301] NaBH₃CN (0.25 mmol) was added to a mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl) glycyl)]aminomethyl]piperidine (0.050 mmol) with 5-bromo-2-ethoxybenzaldehyde (0.15 mmol), methanol (1.2 mL) and acetic acid (0.030 mL). The resulting mixture was stirred at 50 °C for 13 hours, cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol (5 mL×3). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. Dichloromethane (1 mL) and trifluoroacetic acid (0.50 mL) were added to the resulting residue, and the mixture was stirred at room temperature for 10 minutes. The reaction mixture was concentrated, and the residue was dissolved in methanol. The resulting solution was loaded onto a Varian™ SCX column and washed with methanol (5 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃(5 mL), concentrated and purified by preparative TLC (SiO₂, ethyl acetate/methanol = 10:1) to provide 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(5-bromo-2-ethoxybenzyl)piperidine (Compd. No. 2052) (10.2 mg, 38%). The purity was determined by RPLC/MS (96%). ESI/MS m/e 539.2 (M*+H, C₂₄H₂₉BrF₂N₄O₃).

[Examples 1785 to 1792]

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[0302] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1784. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 38.

Table 38

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1785	2053	C ₃₀ H ₃₄ F ₂ N ₄ O ₄	553.4	12.7	46
1786	2054	C ₂₇ H ₃₀ F ₂ N ₄ O ₃	497.2	13.7	55
1787	2055	C ₂₃ H ₂₈ F ₂ N ₄ O ₄	463.2	10.1	44
1788	2056	C ₂₂ H ₂₄ BrF ₃ N ₄ O ₂	515.2	7.7	30
1789	2057	C ₂₃ H ₂₇ BrF ₂ N ₄ O ₃	527.0	8.6	33
1790	2058	C ₂₄ H ₃₀ F ₂ N ₄ O ₄	477.2	6.4	27
1791	2059	C ₂₈ H ₃₀ F ₂ N ₄ O ₃	509.4	6.7	26
1792	2060	C ₂₅ H ₃₂ F ₂ N ₄ O ₅	507.2	7.2	28

[Example 1793] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3,4-diethoxybenzyl)piperidine (Compd. No. 2065)

[0303] NaBH₃CN (0.25 mmol) was added to a mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl) glycyl]aminomethyl]piperidine (0.050 mmol) with 3,4-diethoxybenzaldehyde (0.15 mol), methanol (1.2 mL) and acetic acid (0.050 mL), and the obtained mixture was stirred at 50 °C overnight, cooled to room temperature, loaded onto a VarianTM SCX column and washed with methanol (5 mL × 2). The obtained product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. Dichloromethane (2 mL) and phenyl isocyanate (0.10 mL) were added to the obtained residue, and the resulting mixture was stirred at room temperature for 1 hour, loaded onto a VarianTM SCX column and washed with methanol (5 mL). The obtained product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. The residue was dissolved in methanol (0.25 mL), and a 4 M dioxane solution of HCl (0.125 mL) was added to the resulting solution. The obtained mixture was stirred at room temperature overnight and concentrated. The resulting residue was dissolved in methanol, loaded onto a VarianTM SCX column and washed with methanol

(5 mL \times 2). The obtained crude product was eluted with a 2 M methanol solution of NH₃(5 mL) and concentrated to thereby afford 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3,4-diethoxybenzyl)piperidine (Compd. No. 2065) (21.2 mg, 84%). The purity was determined by RPLC/MS (97%). ESI/MS m/e 505.2 (M++H, $C_{26}H_{34}F_{2}N_{4}O_{4}$).

[Examples 1794 to 1808]

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[0304] The compounds used in the present invention were synthesized by using the respective corresponding raw materials and reactants according to the method of Example 1793. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 39.

Table 39

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1794	2061	C ₂₃ H ₂₇ F ₃ N ₄ O ₂	449.2	12.6	56
1795	2062	C ₂₃ H ₂₇ F ₃ N ₄ O ₃	465.2	19.7	85
1796	2063	C ₂₅ H ₃₂ F ₂ N ₄ O ₄	491.2	19.8	81
1797	2064	C ₂₂ H ₂₄ BrF ₃ N ₄ O ₂	515.2	17.5	68
1798	2066	C ₂₉ H ₃₂ F ₂ N ₄ O ₃	523.2	18.0	69
1799	2067	C ₂₆ H ₃₄ F ₂ N ₄ O ₂	473.2	21.9	93
1800	2068	C ₂₂ H ₂₄ CIF ₃ N ₄ O ₂	469.2	11.2	48
1801	2069	C ₂₄ H ₃₀ F ₂ N ₄ O ₃	461.4	20.2	88
1802	2070	C ₂₃ H ₂₇ BrF ₂ N ₄ O ₃	527.2	17.7	67
1803	2071	C ₂₄ H ₃₀ F ₂ N ₄ O ₄	477.2	10.9	46
. 1804	2072	C ₂₅ H ₃₂ F ₂ N ₄ O ₃	475.2	19.3	81
1805	2073	C ₂₉ H ₃₂ F ₂ N ₄ O ₃	523.2	22.8	87
1806	2074	C ₂₉ H ₃₂ F ₂ N ₄ O ₄	539.2	22.5	84
1807	2075	C ₂₃ H ₂₇ F ₃ N ₄ O ₃	465.2	14.9	64
1808	2076	C ₂₂ H ₂₄ F ₄ N ₄ O ₂	453.2	21.9	97

[Example 1809] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(2-hydroxy-3-methylbenzyl) piperidine (Compd. No. 2106)

[0305] NaBH₃CN (0.40 mmol) was added to a mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl) glycyl]aminomethyl]piperidine (0.050 mmol) with 2-hydroxy-3-methylbenzaldehyde (0.25 mmol), methanol (1.0 mL) and acetic acid (0.040 mL). The resulting mixture was stirred at 50 °C overnight, cooled to room temperature, loaded onto a VarianTM SCX column and washed with methanol (5 mL×2). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. The residue was dissolved in ethyl acetate/methanol = 5:1 (1 mL), loaded onto a VarianTM SCX column, eluted with ethyl acetate/methanol = 5:1 (5 mL) and concentrated. The residue was dissolved in methanol (2 mL), and a 4 M dioxane solution of HCl (0.50 mL) was added to the resulting solution. The obtained mixture was stirred at room temperature overnight and concentrated. The residue was dissolved in methanol, loaded onto a VarianTM SCX column and washed with methanol (5 mL×2). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL), concentrated and purified by preparative TLC to thereby provide 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(2-hydroxy-3-methylbenzyl)piperidine (Compd. No. 2106). The purity was determined by RPLC/MS (97%). ESI/MS m/e 447.0 (M*+H, C₂₃H₂₈F₂N₄O₃).

[Examples 1810 to 1823]

[0306] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1809. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 40.

Table 40

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Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)			
1810	2077	C ₂₂ H ₂₅ CIF ₂ N ₄ O ₃	467.2	3.7	16			
1811	2078	C ₂₄ H ₃₀ F ₂ N ₄ O ₄	477.2	1.9	8			
1812	2079	C ₃₀ H ₃₄ F ₂ N ₄ O ₄	553.4	4.8	17			
1813	2080	C ₂₂ H ₂₅ CIF ₂ N ₄ O ₃	467.2	13.5	58			
1814	2081	C ₂₂ H ₂₅ CIF ₂ N ₄ O ₃	467.2	13.8	59			
1815	2082	C ₂₃ H ₂₈ F ₂ N ₄ O ₄	463.2	9.6	42			
1816	2105	C ₂₃ H ₂₈ F ₂ N ₄ O ₄	463.2	ND	ND			
1817	2106	C ₂₃ H ₂₈ F ₂ N ₄ O ₃	447.0	ND	ND			
1818	2107	C ₂₀ H ₂₃ BrF ₂ N ₄ O ₂ S	503.1	ND	ND			
1819	2108	C ₂₅ H ₂₈ F ₂ N ₄ O ₂ S	487.2	ND	ND			
1820	2109	C ₂₀ H ₂₃ BrF ₂ N ₄ O ₃	487.0	ND	ND			
1821	2110	C ₂₂ H ₂₈ F ₂ N ₄ O ₃	435.1	ND	ND			
1822	2111	C ₂₂ H ₂₄ CIF ₃ N ₄ O ₂	469.0	ND	ND			
1823	2112	C ₂₄ H ₂₉ BrF ₂ N ₄ O ₄	557.0	ND	ND			
Note:	Note: ND means "Not Determined".							

[Example 1824] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3-amino-4-methylbenzyl) piperidine (Compd. No. 2114)

[0307] NaBH₃CN (0.50 mmol) was added to a mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl) glycyl]aminomethyl]piperidine (0.050 mmol) with 4-methyl-3-nitrobenzaldehyde (0.25 mmol), methanol (1.2 mL) and acetic acid (0.050 mL). The resulting mixture was stirred at 50 °C overnight, cooled to room temperature, loaded onto a VarianTM SCX column and washed with methanol (5 mL×2). The obtained product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. The residue was dissolved in ethyl acetate/methanol = 2:1 (2 mL), loaded onto a VarianTM Si column, eluted with ethyl acetate/methanol = 2:1 (6 mL) and concentrated. The obtained residue was dissolved in methanol (1 mL), and a 4 M dioxane solution of HCl (0.50 mL) was added to the resulting solution. The obtained mixture was stirred at room temperature overnight and concentrated. The resulting residue was dissolved in methanol, loaded onto a VarianTM SCX column, washed with methanol (5 mL × 2), then eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated to thereby afford 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(4-methyl-3-nitrobenzyl)piperidine.

[0308] A mixture of the resulting 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(4-methyl-3-nitrobenzyl) piperidine with a 5% palladium carbon (15 mg) and methanol (2 mL) was stirred at room temperature under a hydrogen atmosphere for 4 hours. The palladium catalyst was removed by filtration through Celite, and the filtrate was concentrated and purified by preparative TLC (SiO₂, ethyl acetate/methanol = 3:1) to thereby provide 4-[[N-(2-amino-4, 5-difluorobenzoyl)glycyl]aminomethyl]-1(3-amino-4-methylbenzyl)piperidine (Compd. No. 2114) (2.9 mg, 13%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 446.1 (M++H, $C_{23}H_{29}F_2N_5O_2$).

[Example 1825] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3-amino-4-methoxybenzyl) piperidine (Compd. No.2113)

[0309] The title compound 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3-amino-4-methoxybenzyl) piperidine (Compd. No. 2113) was synthesized by using the corresponding starting material and reactants according to the method of Example 1824. 4.6 mg, 20% yield; ESI/MS m/e 462.2 (M++H, $C_{23}H_{29}F_2N_5O_3$).

[Example 1826] Synthesis of 1-(3-amino-4-hydroxybenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl) glycyl]aminomethyl]piperidine

[0310] A methanol (3.2 mL) solution of NaBH₃CN (1.58 mmol) was added to a mixture of 4-[[N-(2-(tert-butoxycarb-

onylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (0.35 mmol) with 4-hydroxy-3-nitrobenzaldehyde (1.22 mmol), methanol (3.8 mL) and acetic acid (0.175 mL), and the resulting mixture was stirred at 50 °C overnight, cooled to room temperature, loaded onto a Varian™ SCX column and washed with methanol (5 mL × 2). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. The residue was dissolved in ethyl acetate/methanol = 5:1, loaded onto a Varian™ Si column, eluted with ethyl acetate/methanol = 5:1 (10 mL) and concentrated to thereby afford 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(4-hydroxy-3-nitrobenzyl)piperidine (175 mg, 87%).

[0311] A mixture of the resulting 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(4-hydroxy-3-nitrobenzyl)piperidine with a 10% palladium carbon (45 mg) and methanol (5 mL) was stirred at room temperature under a hydrogen atmosphere for 4 hours. The palladium catalyst was removed by filtration, and the filtrate was concentrated to provide 1-(3-amino-4-hydroxybenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl) glycyl]aminomethyl]piperidine (100 mg, 60%).

[Example 1827] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3-amino-4-hydroxybenzyl) piperidine (Compd. No. 2141)

[0312] A 4 M dioxane solution of HCI (0.50 mL) was added to a methanol (1 mL) solution of 1-(3-amino-4-hydroxybenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (20.0 mg, 0.035 mmol), and the resulting mixture was stirred at room temperature overnight and concentrated. The obtained residue was then dissolved in methanol, loaded onto a VarianTM SCX column, washed with methanol (5 mL \times 2), eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated to thereby afford 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl] aminomethyl]-1-(3-amino-4-hydroxybenzyl)piperidine (Compd. No. 2141) (17.6 mg, quantitative). The purity was determined by RPLC/MS (85%). ESI/MS m/e 448.3 (M++H, $C_{22}H_{27}F_2N_5O_3$).

[Examples 1828 to 1831]

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[0313] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the methods of Examples 1826 and 1827. The obtained products, if necessary, were purified by preparative TLC to provide the objective compounds. Data of ESIIMS and yields (mg) and yields (%) in the final steps are collectively shown in Table 41.

	Table 41							
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)			
1828	2140	C ₂₃ H ₂₇ F ₂ N ₅ O ₄	476.3	6.7	28.4			
1829	2144	C ₂₄ H ₃₀ F ₃ N ₅ O ₃	494.2	18.7	82.0			
1830	2145	C ₂₃ H ₂₈ F ₃ N ₅ O ₃	480.3	19.8	63.7			
1831	2146	C ₂₄ H ₂₈ F ₃ N ₅ O ₄	508.3	13.5	81.7			

Table 41

[Example 1832] Synthesis of 1-(3-amino-4-chlorobenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl) glycyl]aminomethyl]piperidine

[0314] A methanol (1.3 mL) solution of NaBH₃CN (0.63 mmol) was added to a mixture of 4-[[N-(2-(tert-butoxycarb-onylamino)-4,5-diffuorobenzoyl)glycyl]aminomethyl]piperidine (0.14 mmol) with 4-chloro-3-nitrobenzaldehyde (0.50 mmol), methanol (1.5 mL) and acetic acid (0.070 mL). The resulting mixture was stirred at 50 °C overnight, cooled to room temperature, loaded onto a Varian[™] SCX column and washed with methanol. The obtained product was eluted with a 2 M methanol solution of NH₃ and concentrated. The residue was dissolved in ethyl acetate/methanol = 5:1, loaded onto a Varian[™] Si column, eluted with ethyl acetate/methanol = 5:1 (6 mL) and concentrated to thereby provide 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(4-chloro-3-nitrobenzyl)piperidine (44 mg, 53%). ESI/MS m/e 596.3 (M++H).

[0315] A mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(4-chloro-3-ni-trobenzyl)piperidine (121 mg, 0.20 mmol) with a 10% palladium carbon (85 mg), ethyl acetate (10 mL) and methanol (1 mL) was stirred at room temperature under a hydrogen atmosphere for 19 hours. The palladium catalyst was removed by filtration, and the filtrate was concentrated to thereby afford 1-(3-amino-4-chlorobenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (78 mg, 68%).

[Example 1833] Synthesis of 1-(3-amino-4-chlorobenzyl)-4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl] piperidine (Compd. No. 2142)

[0316] The title compound 1-(3-amino-4-chlorobenzyl)-4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (Compd. No. 2142) was synthesized by using the corresponding starting material and reactants according to the method of Example 1827. 13.7 mg, 98%. The purity was determined by RPLC/MS (83%). ESI/MS m/e 466.2 (M++H, C₂₂H₂₆CIF₂N₅O₂).

[Example 1834] Synthesis of 1-(3-acetylamino-4-hydroxybenzyl)-4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl] aminomethyl]piperidine (Compd. No. 2148)

[0317] A dichloromethane (0.12 mL) solution of acetic anhydride (0.12 mmol) was added to a mixture of 1-(3-amino-4-hydroxybenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (27 mg, 0.049 mmol) with a (piperidinomethyl)polystyrene (2.7 mmol/g, 60 mg, 0.15 mmol) and dichloromethane (2 mL), and the resulting mixture was stirred at room temperature for 3 hours. The mixture was loaded onto a Varian™ SCX column and washed with methanol. The obtained crude product was eluted with a 2 M methanol solution of NH₃ and concentrated. The residue was dissolved in ethyl acetate/methanol = 5:1, loaded onto a Varian™ Si column, eluted with ethyl acetate/methanol = 5:1 (6 mL) and concentrated to thereby provide 1-(3-acetylamino-4-hydroxybenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (30 mg, quantitative). ESI/MS m/e 590.4 (M*+H, C₂₉H₃₇N₅O₆).

[0318] A 4 M dioxane solution of HCI (0.50 mL) was added to a methanol (1 mL) solution of the 1-(3-acetylamino-4-hydroxybenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine obtained above, and the resulting solution was stirred at room temperature overnight and concentrated. The resulting residue was then dissolved in methanol, loaded onto a VarianTM SCX column, washed with methanol (5 mL \times 2), eluted with a 2 M methanol solution of NH₃ (5 mL), concentrated and then purified by preparative TLC (SiO₂, ethyl acetate/methanol = 3:2) to thereby afford 1-(3-acetylamino-4-hydroxybenzyl)-4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl] piperidine (Compd. No. 2148) (2.3 mg, 9.2%). The purity was determined by RPLC/MS (98%). ESI/MS m/e 490.3 (M++H, $C_{24}H_{29}F_2H_5O_4$).

30 [Examples 1835 to 1839]

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[0319] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the methods of Examples 1826 and 1834. Data of ESI/MS and yields (mg) and yields (%) in the final steps are collectively shown in Table 42.

Table 42

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1835	2143	C ₂₅ H ₂₉ F ₂ N ₅ O ₅	518.3	4.8	45
1836	2147	C ₂₅ H ₃₁ F ₂ N ₅ O ₄	504.3	3.0	23
1837	2154	C ₂₆ H ₃₂ F ₃ N ₅ O ₄	536.4	4.1	66
1838	2155	C ₂₅ H ₃₀ F ₃ N ₅ O ₄	522.3	5.5	71
1839	2156	C ₂₆ H ₃₀ F ₃ N ₅ O ₅	550.3	7.0	78

[Example 1840] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3-methylamino-4-hydroxybenzyl)piperidine (Compd. No. 2160)

[0320] A methanol (0.2 mL) solution of NaBH₃CN (7.0 mg) was added to a mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3-amino-4-hydroxy)piperidine (20.4 mg, 0.037 mmol) with a 37% HCHO solution (3.0 mg, 0.037 mmol), acetic acid (0.1 mL) and methanol (1.3 mL), and the resulting mixture was stirred at 60 °C overnight, cooled to room temperature, loaded onto a VarianTM SCX column and washed with methanol (5 mL× 2). The obtained crude product was eluted with a 2 M methanol solution of NH3 (8 mL) and concentrated to thereby provide 4-[[N-(2-tert-butoxycarbonylamino)-4,5-difluorobenzoyl]glycyl]aminomethyl]-1-(3-methylamino-4-hydroxybenzyl)piperidine.

[0321] A 4 M dioxane solution of HCl (1.0 mL) was added to a methanol (1.0 mL) solution of the 4-[[N-(2-tert-butox-ycarbonylamino)-4,5-difluorobenzoyl]glycyl]aminomethyl]-1-(3-methylamino-4-hydroxybenzyl)piperidine obtained

above, and the resulting mixture was stirred at room temperature for 3 hours and concentrated. The obtained residue was then dissolved in methanol (1 mL), loaded onto a Varian™ SCX column, washed with methanol (5 mL×2), eluted with a 2 M methanol solution of NH₃(8 mL), concentrated and then purified by preparative TLC (SiO₂) to thereby afford 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3-methylamino-4-hydroxybenzyl)piperidine (Compd. No. 2160) (3.4 g, 20%). The purity was determined by RPLC/MS (96%). ESI/MS m/e 462.4 (M++H, C₂₃H₂₉F₂N₅O₃).

[Examples 1841 to 1844]

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[0322] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the methods of Examples 1826 and 1840. Data of ESI/MS and yields (mg) and yields (%) in the final steps are collectively shown in Table 43.

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Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1841	2159	C ₂₄ H ₃₁ F ₂ N ₅ O ₃	476.3	7.6	48
1842	2161	C ₂₃ H ₂₈ CIF ₂ N ₅ O ₂	480.3	7.3	45
1843	2162	C ₂₅ H ₃₂ F ₃ N ₅ O ₃	508.4	6.0	24
1844	2163	C ₂₄ H ₃₀ F ₃ N ₅ O ₃	494.3	4.3	15

[Example 1845] Synthesis of 4-[[N-(2-amino-4, 5-difluorobenzoyl)glycyl]aminomethyl]-1-(benzo[c]furazan-5-yl) piperidine (Compd. No. 2130)

25 [0323] A mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (0.050 mmol) with 5-(bromomethyl)benzo[c]furazan (0.75 mL), a (piperidinomethyl)polystyrene (2.6-2.8 mmol/a, 60 mg, 0.15 mmol), methanol (0.2 mL), acetonitrile (1.0 mL) and chloroform (0.50 mL) was stirred at 50 °C overnight, cooled to room temperature, loaded onto a VarianTM SCX column and washed with methanol (5 mL \times 2). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. Chloroform (1.5 mL) and phenyl 30 isocyanate (0.075 mL) were added to the residue, and the resulting mixture was stirred at room temperature for 1 hour, loaded onto a VarianTM SCX column and washed with methanol (5 mL × 2). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. The resulting residue was dissolved in methanol (1 mL), and a 4 M dioxane solution of HCI (0.50 ml) was added to the obtained solution. The resulting mixture was stirred at room temperature overnight and concentrated. The residue was then dissolved in methanol, loaded onto a Varian™ 35 SCX column, washed with methanol (5 mL \times 2), eluted with a 2 M methanol solution of NH₃ (5 mL), concentrated and then purified by preparative TLC (SiO2, ethyl acetate/methanol = 5:1) to provide 4-[[N-(2-amino-4,5-difluorobenzoyl) glycyl]aminomethyl]-1-(benzo[c]furazan-5-yl)piperidine (Compd. No. 2130) (3.6 mg, 16%). The purity was determined by RPLC/MS (87%): ESI/MS m/e 459.3 (M++H, C₂₂H₂₄F₂N₆O₃).

[Example 1846] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3,5-dimethylisoxazol-4-yl) piperidine (Compd. No. 2131)

[0324] The title compound 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(3,5-dimethylisoxazol-4-yl)piperidine (Compd. No. 2131) was synthesized by using the corresponding starting material and reactants according to the method of Example 1845. 3.8 mg, 18% yield; ESI/MS m/e 436.2 (M++H, $C_{21}H_{27}F_2N_5O_3$).

[Example 1847] Synthesis of 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]aminomethyl]-1-[4-(trifluoromethylthio)benzyl] piperidine (Compd. No. 1616)

[0325] A mixture of 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]aminomethyl]piperidine (16.2 mg, 0.050 mmol) with 4-(tri-fluoromethylthio)benzyl chloride (20.3 mg, 0.075 mmol), acetonitrile (1.0 mL) and chloroform (0.50 mL) was stirred at 60 °C for 15 hours, cooled, then loaded onto a VarianTM SCX column and washed with methanol (15 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated to thereby afford 4-[[N-(2-amino-5-chlorobenzoyl)glycyl]aminomethyl]-1-[4-(trifluoromethylthio)benzyl]piperidine (Compd. No. 1616) (21.9 mg, 85%).
 The purity was determined by RPLC/MS (96%). ESI/MS m/e 545.2 (M++H, C₂₃H₂₆CIF₃N₄O₂S).

[Examples 1848 to 1868]

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[0326] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1847. The obtained products, if necessary, were purified by preparative TLC to provide the objective compounds. Data of ESI/MS and yields (mg) and yields (%) in the final steps are collectively shown in Table 44.

Table 44

Table 44							
Example	Compd. No.	Molecular Formula .	ESI/MS m/e	Yield (mg)	Yield (%)		
1848	1617	C ₂₃ H ₂₆ BrF ₃ N ₄ O ₂ S	559.0	21.0	75		
1849	1777	C ₂₃ H ₂₅ Cl ₂ F ₈ N ₄ O ₂	517.0	16.3	63.0		
1850	1778	C ₂₄ H ₂₉ F ₃ N ₄ O ₂	463.2	9.5	41.1		
1851	1779	C ₂₄ H ₂₇ F ₃ N ₄ O ₄	493.2	12.7	51.6		
1852	1780	C ₂₃ H ₂₆ BrF ₃ N ₄ O ₂	527.0	16.4	62.2		
1853	1781	C ₂₃ H ₂₇ F ₃ N ₄ O ₃	465.2	10.0	28.7		
1854	1782	C ₂₅ H ₂₉ F ₃ N ₄ O ₂	475.2	12.2	34.3		
1855	1783	C ₂₄ H ₂₆ F ₃ N ₅ O ₂	474.2	17.2	48.4		
1856	1784	C ₂₃ H ₂₇ F ₃ N ₄ O ₂	449.2	11.3	33.6		
1857	1788	C ₂₅ H ₃₁ F ₃ N ₄ O ₂	477.2	10.0	42.0		
1858	1789	C ₂₄ H ₂₉ F ₃ N ₄ O ₃	479.2	10.0	27.9		
1859	1792	C ₂₄ H ₃₀ F ₂ N ₄ O ₂	445.2	5.9	26.5		
1860	1793	C ₂₂ H ₂₄ Cl ₂ F ₂ N ₄ O ₂	485.2	9.2	37.9		
1861	1794	C ₂₃ H ₂₈ F ₂ N ₄ O ₂	431.2	5.7	26.5		
1862	1795	C ₂₃ H ₂₆ F ₂ N ₄ O ₄	461.2	6.0	26.1		
1863	1796	C ₂₂ H ₂₅ BrF ₂ N ₄ O ₂	497.0	10.5	42.4		
1864.	1797	C ₂₂ H ₂₆ F ₂ N ₄ O ₃	433.2	3.5	16.2		
1865 -	1798	C ₂₃ H ₂₈ F ₂ N ₄ O ₃	447.2	5.6	25.1		
1866	1799	C ₂₄ H ₂₈ F ₂ N ₄ O ₂	443.2	5.5	24.9		
1867	1800	C ₂₃ H ₂₅ F ₂ N ₅ O ₂	442.2	9.4	42.6		
1868	1801	C ₂₂ H ₂₆ F ₂ N ₄ O ₂	417.2	6.5	31.2		

[Example 1869] Synthesis of 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]aminomethyl]-1-(4-bromobenzyl) piperidine (Compd. No. 1910)

[0327] A mixture of 4-[[N-(2-tert-butoxycarbonylamino)-5-trifluoromethoxybenzoyl]glycyl]aminomethyl]piperidine (0.050 mmol) with 4-bromobenzyl bromide (0.060 mmol), a piperidinomethylpolystyrene (60mg), acetonitrile (0.8 mL) and chloroform (0.5 mL) was stirred at 60 °C for 12 hours, cooled, then loaded onto a Varian™ SCX column and washed with a 50% chloroform/methanol (10 mL) and methanol (10 mL). The obtained product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. A 4 M 1, 4-dioxane solution of HCl (2 mL) was added to the resulting residue, and the obtained mixture was stirred at room temperature overnight, concentrated and then purified by preparative TLC to thereby provide 4-[[N-(2-amino-5-trifluoromethoxybenzoyl)glycyl]aminomethyl]-1-(4-bromobenzyl)piperidine (Compd. No. 1910) (6.5 mg, 24%). The purity was determined by RPLC/MS (96%). ESI/MS m/e 545 (M++H, C₂₃H₂₆BrF₃N₄O₃).

[Examples 1870 to 1873]

[0328] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1869. Data of ESI/MS and yields (mg) and yields (%) in

the final steps are collectively shown in Table 45.

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Table 45

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1870	1911	C ₂₃ H ₂₅ Cl ₂ F ₃ N ₄ O ₃	533	10.6	39.7
1871	1912	C ₂₃ H ₂₇ F ₃ N ₄ O ₄	481	12.5	52.0
1872	1913	C ₂₅ H ₃₁ F ₃ N ₄ O ₃	493	7.5	30.5
1873	1914	C ₂₄ H ₂₉ F ₃ N ₄ O ₃	479	11.0	46.0

[Example 1874] Synthesis of 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]aminomethyl]-1-(benz[d]imidazol-5-yl) piperidine (Compd. No. 2186)

[0329] A mixture of 4-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]aminomethyl]piperidine (0.060 mmol) with 1-(tert-butoxycarbonyl)-6-(bromomethyl)benz[d]imidazole (15.6 mg, 0.050 mmol), a (piperidinomethyl)polystyrene (86 mg, 0.15 mmol) and acetonitrile (2 mL) was stirred at 50 °C for 3 hours and cooled to room temperature. Phenyl isocyanate (30 mg) was then added to the cooled mixture, and the resulting mixture was stirred at room temperature for 1 hour, loaded onto a Varian™ SCX column and washed with methanol (5 mL) and chloroform (5 mL). The obtained product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated.

[0330] The resulting substance was dissolved in methanol (1 mL), and a 4 M dioxane solution of HCl (1 mL) was added to the obtained solution. The resulting mixture was stirred at room temperature overnight, loaded onto a Varian™ SCX column, washed with methanol (5 mL) and dichloromethane. The resulting product was eluted with a 2 M methanol solution of NH₃ and concentrated. The obtained crude product was purified by preparative TLC (SiO₂, ethyl acetate/ methanol = 3:1) to thereby afford 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]aminomethyl]-1-(benz[d]imidazol-5-yl)piperidine (Compd. No. 2186) (1.9 mg, 7.8%). The purity was determined by RPLC/MS (100%). ESI/Ms m/e 489.4 (M++H, C₂₄H₂₇F₃N₆O₂).

[Example 1875] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(benzo[c]thiadiazol-5-yl) piperidine (Compd. No. 2184)

[0331] Methanesulfonyl chloride (0.0042 mL) was added to a mixture of 5-(hydroxymethyl)benzo[c]thiadiazole (8.3 mg, 0.050 mmol) with a (piperidinomethyl)polystyrene (86 mg) and chloroform (1 mL), and the resulting mixture was stirred at room temperature for 1.5 hours. Acetonitrile (1 mL) and 4-[[(N-(2-(tert-butoxycarbonylamino)-4,5-difluorobenzoyl)glycyl)aminomethyl]piperidine were added to the mixture, and the resulting reaction mixture was stirred at 50 °C for 3 hours and cooled to room temperature. Phenyl isocyanate (30 mg) was then added to the cooled mixture, and the resulting mixture was stirred at room temperature for 1 hour, loaded onto a Varian™ SCX column and washed with methanol (5 mL) and chloroform (5 mL). The product was eluted with a 2 M methanol solution of NH₃ (3 mL) and concentrated. The resulting residue was dissolved in dichloromethane (1 mL), and a dichloromethane (1 mL) solution of chlorotrimethylsilane (1 M) and phenol (1 M) was added to the obtained solution. The resulting mixture was stirred at room temperature for 5 hours, then loaded onto a Varian™ SCX column and washed with methanol and dichloromethane. The obtained crude product was eluted with a 2 M methanol solution of NH₃ and purified by preparative TLC (SiO₂, ethyl acetate/methanol = 3:1) to thereby provide 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(benzo[c]thiadiazol-5-yl)piperidine (Compd. No. 2184) (1.3 mg, 5.5%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 475.2 (M++H, C₂₂H₂₄F₂N₀O₂S).

[Example 1876] Synthesis of 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]aminomethyl]-1-(benzo[c]thiadiazol-5-yl) piperidine (Compd. No. 2185)

[0332] 4-[[N-(2-Amino-5-trifluoromethylbenzoyl)glycyl]aminomethyl]-1-(benzo[c]thiadiazol-5-yl)piperidine (Compd. No. 2185) was synthesized by using the corresponding starting material and reactants according to the method of Example 1875. 7.2 mg, 28% yield; ESI/MS m/e 507.4 (M++H, C₂₃H₂₅F₃N₆O₂S).

[Example 1877] Synthesis of 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl] aminomethyl]-1-(2-amino-4-chlorobenzyl)piperidine (Compd. No. 1919)

[0333] A mixture of 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]aminomethyl]piperidine (0.050 mmol) with 4-chlo-

ro-2-nitrobenzyl chloride (0.050 mmol), a piperidinomethylpolystyrene (60 mg), acetonitrile (1.0 mL) and chloroform (0.7 mL) was stirred at 50 °C overnight, cooled, then loaded onto a VarianTM SCX column and washed with chloroform/ methanol (10 mL) and methanol (10 mL). The obtained product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. Ethanol (3 mL) and a 10% palladium carbon (15 mg) were added to the resulting residue, and the obtained mixture was stirred at room temperature under a hydrogen atmosphere for 1.5 hours and filtered. The filtrate was concentrated and then purified by preparative TLC to thereby afford 4-[[N-(2-amino-5-trifluoromethylbenzoyl)gly-cyl]aminomethyl]-1-(2-amino-4-chlorobenzyl)piperidine (Compd. No. 1919) (5.1 mg, 14%). The purity was determined by RPLC/MS (90%). ¹H NMR (400MHz, CDCl₃) δ 1.09-1.32 (m, 4H), 1.41-1.59 (m, 1H), 1.66 (d, J = 12.5 Hz, 2H), 1.88 (t, J= 11.5 Hz, 2H), 2.82 (d, J = 11.5 Hz, H), 3.17 (t. J = 6.5 Hz, 2H), 3.42 (s, 2H), 4.05 (d, J = 3.5 Hz, 2H), 4.85 (br s, 1H), 5.92 (br s, 2H), 6.25-6.36 (m, 1H), 6.55-6.66 (m, 1H), 6.70 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 7.26 (s, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.68 (s, 1H); ESI/MS m/e 498.2 (M++H, C₂₃H₂₇CIF₃N₅O₂).

[Examples 1878 to 1879]

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[0334] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1877. Data of ESI/MS and yields (mg) and yields (%) in the final steps are collectively shown in Table 46.

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Example	Compd. No	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1878	1920	C ₂₂ H ₂₆ CIF ₂ N ₅ O ₂	466.2	3.5	10.0
1879	1922	C ₂₃ H ₂₇ CIF ₃ N ₅ O ₃	514.2	1.2	3.1

[Example 1880] Synthesis of 4-[[N-(2-amino-5-trifluoromethylbenzoyl)glycyl]aminomethyl]-1-(benz[d]oxazol-5-yl) piperidine (Compd. No. 2188)

[0335] Triethyl orthoformate (0.033 mL, 3.3 equivalents) and pyridinium p-toluenesulfonate (2 mg, 0.4 equivalent) were added to a THF (2 mL) solution of 1-(3-amino-4-hydroxybenzyl)-4-[[N-(2-(tert-butoxycarbonylamino)-5-trifluoromethylbenzoyl)glycyl]aminomethyl]piperidine (34.8 mg, 0.060 mL) synthesized according to the method of Example 1826. The resulting mixture was stirred under reflux overnight and cooled to room temperature. The obtained mixture was then concentrated, and the resulting residue was dissolved in ethyl acetate, loaded onto a Bond Elut™ Si column, eluted with ethyl acetate/methanol = 4:1 and concentrated.

[0336] The obtained residue was dissolved in ethyl acetate (1.5 mL), and a 4 M dioxane solution of HCI (0.5 mL) was added to the obtained solution. The resulting mixture was stirred at room temperature overnight, then adjusted to pH10 with a 5 M aqueous solution of NaOH and extracted with ethyl acetate. The extracts was concentrated and purified by preparative TLC (SiO₂, ethyl acetate/methanol = 4:1) to thereby provide 4-[[N-(2-amino-5-trifluoromethyl-benzoyl)glycyl]aminomethyl]-1-(benz[d]oxazol- 5-yl)piperidine (Compd. No. 2188) (1.6 mg, 5%). The purity was determined by RPLC/MS (94%). ESI/MS m/e 490.3 (M++H, $C_{24}H_{26}F_3N_5O_3$).

[Example 1881] Synthesis of 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)piperidine (Compd. No. 2190)

[0337] Phenyl chloroformate (0.040 mL) was added to a mixture of 1-(3-amino-4-hydroxy)-4-[[N-(2-(tert-butoxycar-bonylamino)-4,5-difluorobenzoyl)glycyl]aminomethyl]piperidine (22 mg, 0.040 mmol) with NaHCO₃ (0.040 mmol), water (0.7 mL) and methanol (1.5 mL), and the resulting mixture was stirred at room temperature for 3 hours. A 1 M aqueous solution of NaOH (0.040 mL) was added, and the obtained mixture was further stirred for 1.5 hours. The mixture was then extracted with ethyl acetate, and the extracts was concentrated. The resulting residue was dissolved in methanol, loaded onto a Varian™ SCX column and washed with methanol (5 mL×2). The obtained product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. A dichloromethane (2 mL) solution of chlorotrimethylsilane (1 M) and phenol (1 M) was added to the obtained residue. The mixture was stirred at room temperature for 2 hours and concentrated. The resulting residue was dissolved in methanol, loaded onto a Varian™ SCX column and washed with methanol (5 mL × 2). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL), concentrated and purified by preparative TLC (SiO₂, ethyl acetate/methanol = 5:2) to thereby afford 4-[[N-(2-amino-4,5-difluorobenzoyl)glycyl]aminomethyl]-1-(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)piperidine (Compd. No. 2190) (4.1 mg, 22%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 474.2 (M++H, C₂₃H₂₅F₂N₅O₄).

[Examples 1882 to 1884]

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[0338] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 1881 (phenyl chlorothioformate was used in place of the phenyl chloroformate for synthesizing Compd. Nos. 2192 and 2193). Data of ESI/MS and yields (mg) and yields (%) in the final steps are collectively shown in Table 47.

Table 47

Example	Campa: No.	Chemical Formula	ESI/MS nve	Yleld (mg)	Yield (%)
1882	2191	C24H28F3N5O4	506.3	3.1	10
1883	2192	C ₂₃ H ₂₅ F ₂ N ₅ O ₃ S	490.2	6.9	35
1884	2193	C ₂₄ H ₂₆ F ₃ N ₅ O ₃ S	522.2	3.6	11

[Reference Example 36] 4-[[N-(1-(9-fluorenylmethoxycarbonyl)piperidin-4-ylmethyl)carbamoylmethyl[aminomethyl]-3-methoxyphenyloxymethylpolystyrene

[0339] Acetic acid (0.9 mL), sodium triacetoxyborohydride (1.92 g) and 4-formyl-3-(methoxyphenyloxymethyl)-polystyrene (1 mmol/g, 200 g) were added to a DMF (65 mL) solution of 1-(9-fluorenylmethoxycarbonyl)-4-(glycylaminomethyl)piperidine hydrochloride (10 mmol), and the resulting mixture was shaken for 2 hours and then filtered. The resinwas washed with methanol, DMF, dichloromethane and methanol and dried to provide the objective substance.

[Examples 1885 to 2000] Solid-phase synthesis of 4-aminomethylpiperidines

[0340] Diisopropylethylamine (3.6 mmol) was added to a mixture of the corresponding carboxylic acid (1.6 mmol) with HBTU (1.6 mmol) and DMF (6 mL), and the resulting mixture was shaken for 2 minutes: 4-[[N-(1-(9-Fluorenylmeth-oxycarbonyl)piperidin-4-ylmethyl)carbamoylmethyl[aminomethyl]-3-methoxyphenyloxymethylpolystyrene (0.4 mmol) was added to the resulting mixture, and the obtained mixture was shaken for 1 hour and filtered. The resin was washed with dichloromethane and dried.

[0341] A mixture of NaBH(OAc)₃ (0.25 mmol) with acetic acid (0.025 mmol) and DMF was added to the obtained resin (0.05 mmol), and the corresponding aldehyde (2.5 mmol) was further added. The resulting mixture was shaken for 2 hours, then littered and washed with methanol, a 10% DMF solution of disopropylethylamine, DMF, dichloromethane and methanol. A mixture of the resin with water (0.050 mL) and trifluoroacetic acid (0.95 mL) was shaken for 1 hour and filtered. The resin was washed with dichloromethane and methanol. The filtrate and washings were combined and concentrated. The resulting residue was loaded onto a Varian^{1M} SCX column and washed with methanol (15 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated. The obtained product, if necessary, was purified by preparative TLC or HPLC to provide the objective compounds. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 48.

Table 48

Example	Compd. No.	Molecular Formula.	ESI/MS nve	Yield (mg)	Yield (%)
1885	1923	C ₂₃ H ₂₅ BrF ₃ N ₃ O ₂ S	544	15.7	87
1886	1924	C ₂₄ H ₂₈ F ₃ N ₃ O ₈ S	496	14.6	89
1887	1925	C ₂₃ H ₂₅ F ₄ N ₃ O ₂ S	484	11.7	73
1888	1926	C ₂₃ H ₂₄ F ₃ N ₃ O ₂ S	502	13.9	84
1889	1927	C ₂₃ H ₂₅ F ₃ N ₃ O ₃ S	482	10.7	67
1890	1928	C ₂₄ H ₂₆ F ₃ N ₃ O ₄ S	510	14.3	85
1891	1929	C ₂₆ H ₃₀ F ₃ N ₃ O ₂ S	508	14.7	88
1892	1930	C ₂₄ H ₂₈ F ₃ N ₃ O ₂ S ₂	512	14.4	85
1893	1931	C ₂₅ H ₃₀ F ₃ N ₃ O ₂ S	494	14.3	88
1894	1932	C ₂₅ H ₂₈ F ₃ N ₃ O ₃ S	509	7,14	35

Table 48 (continued)

		Table 40 (COIII	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		
Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1895	1933	C ₂₅ H ₃₀ F ₃ N ₃ O ₂ S	494	14.3	88
1896	1934	C ₂₆ H ₃₂ F ₃ N ₃ O ₂ S	509	14.4	86
1897	1935	C ₂₃ H ₂₅ F ₃ N ₄ O ₄ S	511	14.9	88
1898	1936	C ₂₄ H ₂₈ F ₃ N ₃ O ₂ S	480	13.3	84
1899	1937	C ₂₆ H ₃₂ F ₃ N ₃ O ₂ S	509	11.1	66
1900	1938	C ₂₃ H ₂₇ Br ₂ N ₃ O ₂	538	5.3*	25
1901	1939	C ₂₄ H ₃₀ BrN ₃ O ₃	488	5.0*	25
1902	1940	C ₂₃ H ₂₇ BrFN ₃ O ₂	476	4.9*	25
1903	1941	C ₂₃ H ₂₆ BrF ₂ N ₃ O ₂	494	6.1*	30
1904	1942	C ₂₃ H ₂₈ BrN ₃ O ₃	474	1.7*	9
1905	1943	C ₂₄ H ₂₃ BrN ₃ O ₄	502	6.6*	32
1906	1944	C ₂₆ H ₃₂ BrN ₃ O ₂	498	7.0*	35
1907	1945	C ₂₄ H ₃₀ BrN ₃ O ₂ S	504	11.1	67
1908	1946	C ₂₅ H ₃₂ BrN ₃ O ₂	488	3.2*	16
1909	1947	C ₂₅ H ₃₀ BrN ₃ O ₃	500	5.7	35
1910	1948	C ₂₅ H ₃₂ BrN ₃ O ₂	486	4.9*	25
1911	1949	C ₂₆ H ₃₄ BrN ₃ O ₂	500	6.7*	33
1912	1950	C ₂₃ H ₂₇ BrN ₄ O ₄	503	5.0*	25
1913	1951	C ₂₄ H ₃₀ BrN ₃ O ₂	472	5.1*	26
1914	1952	C ₂₂ H ₂₄ Br ₂ FN ₃ O ₂	542	14.9	83
1915	1953	C ₂₃ H ₂₇ BrFN ₃ O ₃	492	13.9	86
1916	1954	C ₂₂ H ₂₄ BrF ₂ N ₃ O ₂	480	12.5	79
1917	1955	C ₂₂ H ₂₃ BrF ₃ N ₃ O ₂	498	13.2	80
1918	1956	C ₂₂ H ₂₅ BrFN ₃ O ₃	478	7.0	44
1919	1957	C ₂₃ H ₂₅ BrFN ₃ O ₄	506	4.0*	20
1920	1958	C ₂₅ H ₂₉ BrFN ₃ O ₂	502	14.6	88
1921	1959	C ₂₃ H ₂₇ BrFN ₃ O ₂ S	508	13.1	78
1922	1960	C ₂₄ H ₂₉ BrFN ₃ O ₂	490	13.8	85
1923	1961	C ₂₄ H ₂₇ BrFN ₃ O ₃	504	2.7*	. 13
1924	1962	C ₂₄ H ₂₉ BrFN ₃ O ₂	490	12.7	78
1925	1963	C ₂₅ H ₃₁ BrFN ₃ O ₂	504	13,5	81
1926	1964	C ₂₂ H ₂₄ BrFN ₄ O ₄	507	14.8	88
1927	1965	C ₂₃ H ₂₇ BrFN ₃ O ₂	476	12.1	77
1928	1966	C ₂₅ H ₃₁ BrFN ₃ O ₂	504	13.4	80
1929	1967	C ₂₂ H ₂₆ BrFN ₄ O ₂	477	4.7*	20
1930	1968	C ₂₃ H ₂₉ FN ₄ O ₃	429	6.9*	32
1931	1969	C ₂₂ H ₂₇ FN ₄ O ₃	415	3.7*	17
1932	1970	C ₂₃ H ₂₇ FN ₄ O ₄	443	5.4*	24

Table 48 (continued)

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Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1933	1971	C ₂₅ H ₃₁ FN ₄ O ₂	439	4.3*	20
1934	1972	C ₂₃ H ₂₉ FN ₄ O ₂ S	445	6.2*	28
1935	1973	C ₂₄ H ₃₁ FN ₄ O ₂	427	6.3*	29
1936	1974	C ₂₄ H ₃₁ FN ₄ O ₂	427	4.9*	23
1937	1975	C ₂₂ H ₂₆ FN ₅ O ₄	444	5.9*	27
1938	1976	C ₂₃ H ₂₉ FN ₄ O ₂	413	6.7*	32
1939	1977	C ₂₃ H ₂₆ FN ₅ O ₂	424	5.1*	24
1940	1978	C25H33FN402	441	6.3*	29
1941	1979	C ₂₅ H ₃₀ F ₂ N ₄ O ₂	457	8.0*	35
1942	1980	C ₂₄ H ₂₈ F ₂ N ₄ O ₃	459	6.0*	26
1943	1981	C ₂₂ H ₂₅ F ₂ N ₅ O ₄	462	9.3*	41
1944	1982	C ₂₃ H ₂₅ F ₂ N ₅ O ₂	442	6.0*	27
1945	1983	C ₂₅ H ₃₂ F ₂ N ₄ O ₂	459	8.3*	37
1946	1984	C ₂₂ H ₂₆ BrlN ₄ O ₂	585	9.7*	36
1947	1985	C ₂₃ H ₂₉ IN ₄ O ₃	537	9.2*	36
1948	1986	C ₂₂ H ₂₇ IN ₄ O ₃	523	5.8*	23
1949	1987	C ₂₃ H ₂₇ IN ₄ O ₄	551	8.2*	32
1950	1988	C ₂₅ H ₃₁ IN ₄ O ₂	547	6.7*	26
1951	1989	C ₂₃ H ₂₉ IN ₄ O ₂ S	553	6.4*	25
1952	1990	C ₂₄ H ₃₁ IN ₄ O ₂	535	7.2*	29
1953	1991	C ₂₄ H ₂₉ IN ₄ O ₃	549	5.6*	22
1954	1992	C ₂₄ H ₃₁ IN ₄ O ₂	535	6.2*	25
1955	1993	C ₂₂ H ₂₆ IN ₅ O ₄	552	. 10.2*	40
1956	1994	C ₂₃ H ₂₉ IN ₄ O ₂	521	7.5*	30
1957	1995	C ₂₃ H ₂₆ IN ₅ O ₂	532	6.8*	27
1958	1996	C ₂₅ H ₃₃ IN ₄ O ₂	549	7.1*	28
1959	1997	C ₂₅ H ₃₃ IN ₄ O ₂	549	3.0*	12
1960	1998	C ₂₂ H ₂₅ BrClN ₃ O ₂	478	7.6*	39
1961	1999	C ₂₃ H ₂₈ CIN ₃ O ₃	430	7.0*	39
1962	2000	C ₂₂ H ₂₅ CIFN ₃ O ₂	418	14.1	102
1963	2001	C ₂₂ H ₂₆ CIN ₃ O ₃	416	6.3*	36
1964	2002	C ₂₃ H ₂₆ CIN ₃ O ₄	444	7.1*	39
1965	2003	C ₂₅ H ₃₀ CIN ₃ O ₂	440	15.3	105
1966	2004	C ₂₃ H ₂₈ ClN ₃ O ₂ S	446	8.4*	45
1967	2005	C ₂₄ H ₃₀ CIN ₃ O ₂	428	7.4*	41
1968	2006	C ₂₄ H ₃₀ CIN ₃ O ₂	428	13.8	98
1969	2007	C ₂₂ H ₂₅ CIN ₄ O ₄	445	16.0	109
1970	2008	C ₂₃ H ₂₈ CIN ₃ O ₂	414	14.1	103

Table 48 (continued)

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
1971	2009	C ₂₃ H ₂₅ CIN ₄ O ₂	425	14.8	106
1972	2010	C ₂₅ H ₃₂ CIN ₃ O ₂	442	14.5	99
1973	2011	C ₂₅ H ₃₂ CIN ₃ O ₂	442	14.5	99
1974	2012	C ₂₂ H ₂₄ Br ₂ CIN ₃ O ₂	558	12.8*	58
1975	2013	C ₂₃ H ₂₇ BrCIN ₃ O ₃	508	8.6*	42
1976	2014	C ₂₂ H ₂₅ BrClN ₃ O ₃	494	6.0*	30
1977	2015	C ₂₃ H ₂₅ BrClN ₃ O ₄	522	8.4*	40
1978	2016	C ₂₅ H ₂₉ BrCIN ₃ O ₂	518	17.6	103
1979	2017	C ₂₃ H ₂₇ BrClN ₃ O ₂ S	524	17.1	99
1980	2018	C ₂₄ H ₂₉ BrClN ₃ O ₂	506	14.7	88
1981	2019	C ₂₄ H ₂₇ BrCIN ₃ O ₃	520	8.0*	38
1982	2020	C ₂₄ H ₂₉ BrClN ₃ O ₂	506	14.7	88
1983	2021	C ₂₂ H ₂₄ BrClN ₄ O ₄	523	12.0*	57
1984	2022	C ₂₃ H ₂₇ BrClN ₃ O ₂	492	8.5*	42
1985	2023	C ₂₃ H ₂₄ BrClN ₄ O ₂	503	6.3*	31
1986	2024	C ₂₅ H ₃₁ BrClN ₃ O ₂	520	9.6*	46
1987	2025	C ₂₅ H ₃₁ BrClN ₃ O ₂	520	15.0	87
1988	2026	C ₂₂ H ₂₃ BrClF ₂ N ₃ O ₂	514	15.8	93
1989	2027	C ₂₂ H ₂₆ Br ₂ N ₄ O ₂	537	10.7*	42
1990	2028	C ₂₃ H ₂₉ BrN ₄ O ₃	489	8.5*	36
1991	2029	C ₂₂ H ₂₇ BrN ₄ O ₃	475	7.5*	32
1992	2030	C ₂₃ H ₂₇ BrN ₄ O ₄	503	6.8*	28
1993	2031	C ₂₅ H ₃₁ BrN ₄ O ₂	499	6.2*	26
1994	2032	C ₂₄ H ₂₉ BrN ₄ O ₃	501	8.9*	37
1995	2033	C ₂₄ H ₃₁ BrN ₄ O ₂	487	9.1*	39
1996	2034	C ₂₂ H ₂₆ BrN ₅ O ₄	504	6.4*	26
1997	2035	C ₂₃ H ₂₉ BrN ₄ O ₂	473	6.5*	28
1998	2036	C ₂₃ H ₂₆ BrN ₅ O ₂	484	6.3*	27
1999	2037	C ₂₅ H ₃₃ BrN ₄ O ₂	501	5.4*	22
2000	2038	C ₂₂ H ₂₅ BrF ₂ N ₄ O ₂	495	5.4*	23

[Example 2001] Synthesis of 1-(3-carbamoylbenzyl)-4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (Compd. No. 924)

[0342] EDCI (10.7 mg), 1-hydroxybenzotriazole hydrate (7.5 mg), triethylamine (15.4 mg), a 0.5 M dioxane solution of NH $_3$ (0.1 mL, 0.05 mmol) and DMF (0.5 mL) were added to a chloroform (2.5 mL) solution of 1-(3-carboxybenzoyl)-4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (19.4 mg, 0.041 mmol), and the resulting mixture was shaken at 25 °C for 20 hours and then washed with a 2 M aqueous solution of NaOH (2 \times 2 mL) and brine (1 mL). The organic layer was filtered through a PTFE membrane filter, and the solvent was then removed under reduced pressure to provide 1-(3-carbamoylbenzyl)-4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (Compd.

No. 924) as an off-white solid (17.9 mg, 92%). The purity was determined by RPLC/MS (89%). ESI/MS m/e 447.3 (M⁺+H, $C_{24}H_{27}F_3N_4O_3$).

[Example 2002] Synthesis of 1-(4-carbamoylbenzyl)-4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (Compd. No. 925)

[0343] The Compd. No. 925 was synthesized by using the corresponding starting material and reactants according to the method of Example 2001. 14.2 mg, 72%. The purity was determined by RPLC/MS (86%). ESI/MS m/e 447 (M^++H , $C_{24}H_{27}F_3N_4O_3$).

[Example 2003] Synthesis of 1-(4-aminobenzyl)-4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (Compd. No. 516)

[0344] An ethanol (3 mL) solution of 1-(4-nitrobenzyl)-4-[[N-(3-trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (22.4 mg, 0.047 mmol) was hydrogenated in the presence of a 5% palladium carbon (10 mg) at 25 °C in a hydrogen atmosphere under 1 atm for 1 hour. The catalyst was removed by filtration, and washed with ethanol (5 mL). The filtrates were collected and concentrated to thereby afford 1-(4-aminobenzyl)-4-[[N-(3-trifluoromethyl)benzoyl]glycyl] aminomethyl]piperidine (Compd. No. 516) as an off-white solid (20.1 mg; 96%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 449.1 (M++H, C₂₃H₂₇F₃N₄O₂).

[Examples 2004 to 2005]

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[0345] Compd. Nos. 517 and 518 were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 2003. Data of ESI/MS and yields (mg) and yields (%) in the final steps are collectively shown in Table 49.

Table 49

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
2004	517	C ₂₃ H ₂₇ F ₃ N ₄ O ₂	449	26.5	78
2005	518	C ₂₃ H ₂₇ F ₃ N ₄ O ₂	449	25.3	71

[Example 2006] Synthesis of 1-[4-(benzoylamino)benzyl]-4-[[N-(3 (trifluoromethyl)benzoyl)glycyl]aminomethyl] piperidine (Compd. No. 519)

[0346] EDCI (4.7 mg), 1-hydroxybenzotriazole hydrate (3.3 mg), triethylamine (2.5 mg) and benzoic acid (3.0 mg) were added to a dichloromethane (2.5 mL) solution of 1-(4-aminobenzyl)-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (10.1 mg, 0.023 mmol), and the resulting mixture was shaken at 25 °C for 16 hours. The reaction mixture was washed with a 2 M aqueous solution of NaOH (2 mL \times 2) and brine (1 mL) and then filtered through a PTFE membrane filter. The solvent was evaporated under reduced pressure to thereby provide yellow oil. The obtained yellow oil was purified by preparative TLC (SiO₂, 10% methanol/dichloromethane) to afford 1-[4-(benzoylamino)benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 519) as a colorless oil (4.6 mg, 36%). The purity was determined by RPLC/MS (99%). ESI/MS mle 553.2 (M++H, $C_{30}H_{31}F_{3}N_{4}O_{3}$).

[Example 2007] Synthesis of 1-[4-(piperidinocarbonyl)benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl] piperidine (Compd. No. 1572)

[0347] Piperidine (0.048 mg), and a DMF (0.15 mL) solution of diisopropylcarbodiimide (0.45 mmol) and 1-hydroxybenzotriazole hydrate (0.45 mmol) were added to a DMF (1.0 mL) solution of 1-(4-carboxybenzyl)-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (0.040 mmol), and the resulting mixture was shaken at room temperature for 17 hours, then loaded onto a Varian™ SCX column and washed with chloroform/methanol = 1:1 (5 mL) and methanol (5 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (5 mL) and concentrated to thereby provide 1-[4-(piperidinocarbonyl)benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyllpiperidine (Compd. No. 1572) (14.3 mg, 66%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 545 (M⁺+H,C₂₉H₃₅F₃N₄O₃).

[Examples 2008 to 2015]

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[0348] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 2007. Data of ESI/MS and yields (mg) and yields (%) in the final steps are collectively shown in Table 50.

Table 50

Example	Compd. No	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
2008	1573	C ₃₁ H ₃₃ F ₃ N ₄ O ₄	583	17.6	76
2009	1574	C ₃₁ H ₃₃ F ₃ N ₄ O ₃	567	18.8	83
2010	1575	C ₃₀ H ₃₀ CIF ₃ N ₄ O ₃	587	3.2	14
2011	1576	C ₂₈ H ₃₃ F ₃ N ₄ O ₄	547	21.1	97
2012	1577	C ₂₆ H ₃₁ F ₃ N ₄ O ₄	521	5.1	24
2013	1578	C ₃₁ H ₃₃ F ₃ N ₄ O ₃	567	16.9	75
2014	1579	C ₃₁ H ₃₃ F ₃ N ₄ O ₃	567	6.0	26
2015	1580	C ₂₉ H ₃₅ F ₃ N ₄ O ₃	545	15.1	69

[Example 2016] Synthesis of 1-[4-(chloroformyl)benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl] piperidine

[0349] A mixture of 1-(4-carboxybenzyl)-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (240 mg) with thionyl chloride (1 mL) was stirred at room temperature for 12 hours, and the excess thionyl chloride was removed under reduced pressure to thereby afford 1-[4-(chloroformyl)benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine. The resulting acid chloride was used without being further purified.

[Example 2017] Synthesis of 1-[4-[N-(2-methoxyethyl)carbamoyl]benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl] aminomethyl]piperidine (Compd. No. 1612)

[0350] A mixture of 1-[4-(chloroformyl)benzyl)-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (0.042 mmol) with 2-methoxyethylamine (3.8 mg, 0.050 mmol), a piperidinomethylpolystyrene (46 mg) and dichloromethane (1.5 mL) was stirred at room temperature for 17 hours. Water (0.020 mL) was then added to the mixture, and the resulting mixture was stirred for 30 minutes. Methanol (1 mL) was then added to the obtained mixture, and the resulting mixture was loaded onto a Varian™ SCX column and washed with methanol (10 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ and concentrated to thereby provide 1-[4-[N-(2-methoxyethyl) carbamoyl]benzyl]-4-[[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 1612) (26.7 mg, 100%). The purity was determined by RPLC/MS (92%). ESI/MS m/e 535.2 (M++H, C₂₇H₃₃F₃N₄O₄).

[Examples 2018 to 2020]

[0351] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to Example 2017. The obtained products, if necessary, were purified by preparative TLC to afford the objective compounds. Data of ESI/MS and yields (mg) and yields (%) are collectively shown in Table 51.

Table 51

Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)		
2018	1610	C ₃₁ H ₃₀ F ₆ N ₄ O ₃	621.2	4.4	14		
2019	1611	C ₃₀ H ₂₉ Cl ₂ F ₃ N ₄ O ₃	621.2	35.7	Q		
2020	1613	C ₃₂ H ₃₅ F ₃ N ₄ O ₃	581.2	29.9	Q		
Note:	Note: Q means "Quantitative".						

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[Example 2021] Synthesis of 4-[N-[5-bromo-2-(methylamino)benzoyl]glycyl]aminomethyl-1-(4-chlorobenzyl)piperidine (Compd. No. 1427)

[0352] A triethyl orthoformate (6.5 mL) solution of 4-[N-(2-amino-5-bromobenzoyl)glycyl]aminomethyl-1-(4-chlorobenzyl)piperidine (Compd. No. 1042) (50 mg, 0.10 mmol) was stirred at 150 °C for 17 hours and concentrated to thereby provide a yellow solid. Sodium borohydride (7.6 mg, 0.2 mmol) was added to an ethanol (3 mL) solution of the yellow solid, and the mixture was stirred at room temperature for 14 hours. The resulting white precipitate was dissolved in dichloromethane, and the obtained solution was washed with a 1 M aqueous solution of NaOH (2 mL). The organic layer was separated, dried over K₂CO₃, filtered and concentrated, and the obtained crude product was purified by column chromatography (SiO₂, 20% methanol/chloroform) to provide 4-[N-[5-bromo-2-(methylamino)benzoyl]glycyl] aminomethyl-1-(4-chlorobenzyl)piperidine (Compd. No. 1427) (40 mg, 80%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 505 (M++H, C₂₃H₂₈BrClF₆N₄O₂).

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[Example 2022] Synthesis of 4-[N-[5-bromo-2-(dimethylamino)benzoyl]glycyl]aminomethyl-1-(4-chlorobenzyl) piperidine (Compd. No. 1428)

[0353] Sodium cyanoborohydride (26 mg, 0.42 mmol) and acetic acid (14 mL) were added to a mixture of 4-[N-(2-amino-5-bromobenzoyl)glycyl]aminomethyl-1-(4-chlorobenzyl)piperidine (Compd. No. 1042) (67 mg, 0.14 mmol) with a 37% aqueous solution of formaldehyde (0.112 mL, 1.4 mmol), acetonitrile (2 mL) and methanol (1.5 mL), and the resulting mixture was stirred at 50 °C for 30 hours. A 1 M aqueous solution of NaOH and dichloromethane were added to the mixture. The aqueous layer was separated, and the organic layer was dried over K_2CO_3 , filtered, concentrated and purified by column chromatography (SiO₂, 20% methanol/ethyl acetate) to afford 4-[N-[5-bromo-2-(dimethylamino) benzoyl]glycyl]aminomethyl-1-(4-chlorobenzyl)piperidine (Compd. No. 1428) (60 mg, 82%). The purity was determined by RPLC/MS (100%). ESI/MS m/e 523 (M*+H, $C_{24}H_{30}BrCIF_6N_4O_2$).

[Example 2023] Synthesis of 4-[[N-[5-bromo-2-(methylsulfonylamino)benzoyl]glycyl]aminomethyl]-1-(4-chlorobenzyl) piperidine (Compd. No. 1581)

[0354] A mixture of 4-[[N-[2-amino-5-bromobenzoyl]glycyl]aminomethyl]-1-(4-chlorobenzyl)piperidine (25 mg, 0.05 mmol) with methanesulfonyl chloride (0.0045 mL), triethylamine (0.026 mL) and dichloromethane (2 mL) was stirred at room temperature for 17 hours. The resulting reaction mixture was purified by column chromatography (SiO₂), loaded onto a VarianTM SAX column and washed with methanol (5 mL). The obtained crude product was eluted with a 0.1 M methanol solution of HCl (5 mL) and concentrated to thereby provide 4-[[N-[5-bromo-2-(methylsulfonylamino)benzoyl] glycyl]aminomethyl]-1-(4-chlorobenzyl)piperidine (Compd. No. 1581) (5.4 mg, 19%). ESI/MS m/e 573.0 (M++H, C₂₃H₂₈BrClN₄O₄S).

[Example 2024] Synthesis of 4-[[N-[5-bromo-2 (bis(methylsulfonyl)amino)benzoyl]glycyl]aminomethyl]-1-(4-chlorobenzyl)piperidine (Compd. No. 1582)

40 [0355] A mixture of 1-(4-chlorobenzyl)-4-[[N-[2-amino-5-bromobenzoyl]glycyl]aminomethyl]piperidine (57 mg, 0.10 mmol) with methanesulfonyl chloride (0.018 mL, 0.024 mmol), triethylamine (0.068 mL) and dichloromethane (2 mL) was stirred at room temperature for 8 hours. A 1 M aqueous solution of NaOH (1 mL) was added to the mixture, and the resulting mixture was extracted with dichloromethane (2 mL × 3). The extracts were combined, dried over K₂CO₃, filtered, concentrated and purified by column chromatography (SiO₂) to afford 4-[[N-[5-bromo-2-(bis(methylsulfonyl) amino)benzoyl]glycyl]aminomethyl]-1-(4-chlorobenzyl)piperidine (Compd. No. 1582) (40 mg, 62%). ESI/MS m/e 651 (M+H, C₂₄H₃₀BrClN₄O₆S₂).

[Example 2025] Synthesis of 1-(4-chlorobenzyl)-1-methyl-4-[[N-[3-(trifluoromethyl)benzoyl]glycyl]aminomethyl] piperidinium iodide (methylammonium iodide of Compd. No. 461)

[0356] An acetonitrile (1.0 mL) solution of 4-[[N-[3-(trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine (30 mg, 0.087 mmol) and a (piperidinomethyl)pblystyrene (80 mg, 2.7 mmol base/g resin) were added to a chloroform (1.0 mL) solution of 4-chlorobenzyl chloride (11.7 mg, 0.073 mmol), and the resulting mixture was stirred at 60 °C for 2 hours. Phenyl isocyanate (10.4 mg, 0.087 mmol) was then added to the reaction mixture cooled to room temperature, and the obtained mixture was stirred at 25 °C for 1 hour, then loaded onto a VarianTM SCX column and washed with methanol (20 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃(6 mL) and concentrated to thereby provide 1-(4-chlorobenzyl)-4-[[N-[3-(trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine as a colorless oil.

[0357] Methyl iodide (28 mg, 0.20 mmol) was added to an acetonitrile (2.0 mL) solution of 1-(4-chlorobenzyl)-

4-[[N-[3-(trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidine. The resulting reaction mixture was stirred at 70 °C for 4 hours. The solvent was removed under reduced pressure to provide 1-(4-chlorobenzyl)-1-methyl-4-[[N-[3-(trifluoromethyl)benzoyl]glycyl]aminomethyl]piperidinium iodide as yellow oil. (31.7 mg, 71%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 482.1 (M++H, $C_{24}H_{28}CIF_3N_3O_2$).

[Example 2026] Synthesis of 1-(4-chlorobenzyl)-4-[N-methyl-N-[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl] piperidine (Compd. No. 520)

[0358] An aqueous solution of formaldehyde (108 mg, 1.33 mmol, 37 wt.%) was added to a 10% acetic acid/methanol (3 mL) solution of 1-(4-chlorobenzyl)-4-(aminomethyl)piperidine (318 mg, 1.33 mmol) and NaBH₃CN (668 mg), and the resulting mixture was stirred at 25 °C for 1 hour. The reaction mixture was loaded onto a Dowex[™] 50Wx2 column (10 mL) and washed with methanol (20 mL). The obtained crude product was eluted with a 2 M methanol solution of NH₃ (6 mL) and concentrated to thereby afford 1-(4-chlorobenzyl)-4-[(methylamino)methyl]piperidine as a colorless oil. The resulting oil was used without being purified.

[0359] EDCI (85 mg) and 1-hydroxybenzotriazole hydrate (60 mg) were added to a dichloromethane (4 mL) solution of 1-(4-chlorobenzyl)-4-[(methylamino)methyl]piperidine (111 mg, 0.44 mmol), and the resulting mixture was stirred at 25 °C for 1 hour, then washed with a 2 M aqueous solution of NaOH (2 mL \times 2) and filtered through a PTFE membrane filter. The solvent was subsequently removed under reduced pressure to provide a yellow oil, which was then purified by preparative TLC to afford 1-(4-chlorobenzyl)-4-[N-methyl-N-[N-(3-(trifluoromethyl)benzoyl)glycyl]aminomethyl]piperidine (Compd. No. 520) as an off-white oil (14.0 mg, 3.4%). The purity was determined by RPLC/MS (99%). ESI/MS m/e 482.1 (M++H, $C_{24}H_{27}CIF_3N_3O_2$).

[Reference Example 37] Synthesis of 3-aminohomopiperidine

[0360] A 1 M BH₃-THF solution (80 mL) was added to a THF (70 mL) solution of DL-α-amino-ε-caprolactam (2 g, 16 mmol), and the resulting mixture was refluxed for 3 hours. A 2 M hydrochloric acid (50 mL) was added, and the reaction mixture was further heated and refluxed for 1 hour and then cooled to 25°C. A 4 M NaOH solution was added to basicify the reaction mixture (pH10), and the resulting mixture was extracted with ethyl acetate (200 mL×3). The organic layers were combined, washed with a saturated aqueous NaHCO₃, dried (over MgSO₄) and concentrated to thereby provide the objective compound (990 mg, 54%). The obtained compounds was used without being purified.

[Reference Example 38] Synthesis of 3-amino-1-(4-chlorobenzyl)homopiperidine

[0361] p-Chlorobenzyl chloride (463 mg, 2.9 mmol) and K₂CO₃ (828 g, 6 mmol) were added to an acetonitrile (45 mL) solution of 3-aminohomopiperidine (1.71 g, 15 mmol), and the resulting mixture was stirred at 70 °C with heating for 9 hours, cooled to 25 °C and concentrated to afford a yellow solid. The resulting residue was partitioned between H₂O (5 mL) and ethyl acetate (50 mL) and the aqueous layer was extracted with ethyl acetate (50 mL×2). The organic layers were combined, washed with brine (20 mL), dried (over MgSO₄) and concentrated. The obtained yellow oil was purified by column chromatography (SiO₂, 5-20% methanol/dichloromethane gradient elution) to afford the objective compounds as yellow oil (639 mg, 93%).

[Example 2027] Synthesis of 1-(4-chlorobenzyl)-3-[(4-benzoylbutyryl)amino]homopiperidine (Compd. No. 994)

[0362] EDCI (23 mg), HOBt (16.2 mg) and triethylamine (15.2 μL) were added to a chloroform (1 mL) solution of 3-amino-1-(4-chlorobenzyl)homopiperidine (24 mg, 0.10 mmol) and 4-benzoylbutyric acid (1.2 equivalents), and the resulting mixture was stirred at 25 °C for 16 hours. The reaction mixture was diluted with dichloromethane (0.5 mL), filtered through a PTFE membrane and concentrated to provide 1-(4-chlorobenzyl)-3-[(4-benzoylbutyryl)amino]homopiperidine (Compd. No. 994) (43 mg, 99%). The purity was determined by RPLC/MS (98%). ESI/MS m/e 413 (M++H, C₂₄H₂₉CIN₂O₂).

[Examples 2028 to 2042]

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[0363] The compounds used in the present invention were synthesized by using the respective corresponding starting materials and reactants according to the method of Example 2027. The obtained products, if necessary, were purified by chromatography (HPLC- C_{18}) to afford the objective compounds as TFA salts. Data of ESI/MS, yields (mg) and yields (%) are collectively shown in Table 52.

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Example	Compd. No.	Molecular Formula	ESI/MS m/e	Yield (mg)	Yield (%)
2028	943	C ₂₃ H ₂₅ CIF ₃ N ₃ O ₂	468	6	28
2029	944	C ₂₃ H ₂₈ CIN ₃ O ₂	414	5	29
2030	945	C ₂₂ H ₂₅ CIN ₄ O ₄	445	6	30
2031	946	C ₂₃ H ₂₇ CIN ₄ O ₄	459	5	24
2032	947	C ₂₅ H ₃₁ CIN ₂ O ₄	459	4	20
2033	.948	C ₂₄ H ₂₉ Cl ₂ N ₃ O ₂	462	6	32
2034	949	C ₂₅ H ₃₂ CIN ₃ O ₂	442	6	31
2035	988	C ₂₃ H ₂₅ CIF ₃ N ₃ O ₂	468	45	92
2036	989	C ₂₃ H ₂₈ CIN ₃ O ₃	430	44	97
2037	990	C ₂₂ H ₂₆ CIN ₃ O ₂	400	41	99
2038	991	C ₂₃ H ₂₇ CIN ₂ O ₂	399	41	97
2039	992	C ₂₅ H ₃₁ CIN ₂ O ₄	459	47	98
2040	993	C ₂₅ H ₃₁ CIN ₂ O ₂	427	44	98
2041	995	C ₂₅ H ₃₁ CIN ₂ O ₃	443	44	95
2042	996	C ₂₄ H ₃₁ CIN ₄ O ₂	443	5*	11
Note: 1	* indicates "yiel	d (mg) of trifluoroaceta	ate".		

[Example 2043] Measurement of inhibitory activity of test compounds against binding of MIP-1α to THP-1 cells

[0364] THP-1 cells which are human monocytic leukemia cell line were suspended in an assay buffer [prepared by adding 0.1% of BSA and 25 mM of HEPES to RPMI-1640 (Gibco-BRL Co.) and adjusting the pH to 7.4] so as to provide 1×10^7 cells/mL to thereby afford a cell suspension. A solution obtained by diluting the test compound with the assay buffer was used as a test compound solution. A solution prepared by diluting an iodine-labeled human MIP-1α (DuPont NEN Co.) with the assay buffer so as to provide 250 nCi/mL was used as a labeled ligand solution. In a 96-well filter plate (Millipore Co.), were aliquoted 25 μL of the test compound solution, 25 μL of the labeled ligand solution and 50 μL of the cell suspension in the order mentioned for each well. The solutions were stirred (100 μL of the reaction solution) and then incubated at 18 °C for 1 hour.

[0365] After completing the reaction, the reaction solution was filtered through a filter, and the filter was washed with 200 μL of cold PBS twice (the reaction solution was filtered after adding 200 μL of the cold PBS). The filter was airdried, and 25 µL of liquid scintillator was then added into each well to count the radioactivity retained by the cells on the filter using TopCount (Packard Instrument Co.).

[0366] The count when 100 ng of an unlabeled human MIP-1α (Peprotech Co.) instead of the test compound was added was subtracted as nonspecific adsorption, and the count when the test compound was not added was taken as 100%. Thereby, the inhibitory activity of the test compound against binding of the human MIP-1 α to THP-1 cells was calculated.

Inhibition ratio (%) =
$$[1-(A-B)/(C-B)] \times 100$$

50 (wherein A is the count when the test compound is added; B is the count when 100 ng of the unlabeled human MIP- 1α is added; C is the count when only the [1251]-labeled human MIP-1 α is added).

[0367] When the inhibitory activity of the cyclic amine derivatives which are active ingredients of the present invention was measured, for example, the following compounds respectively manifested an inhibitory activity of 20% to 50%, 50% to 80% and >80% at a concentration of 2 μ M or 10 μ M.

55 [0368] Compounds which manifested an inhibitory activity of 20% to 50% at a concentration of 10 μM:

230, 231, 233, 234, 236, 237, 238, 333, 334, 335, 336, 338, 340, 342, 347, 348, 349, 350, 352, 357, 359, 361, 366, 372, 374, 375, 376, 380, 382, 383, 385, 470, 471, 472, 473, 474, 483, 484, 488, 489, 491, 497, 499, 500, 502, 506, 508, 510, 514, 515, 518, 524, 543, 553, 554, 555, 556, 563, 571, 575, 576, 578, 579, 580, 583, 586, 587, 588, 590, 591, 592, 595, 596, 598, 603, 610, 611, 612, 614, 624, 625, 626, 629, 635, 638, 639, 640, 641, 642, 643, 644, 646, 647, 648, 649, 652, 653, 658, 659, 660, 665, 666, 669, 671, 675, 677, 679, 681, 682, 684, 691, 695, 696, 700, 702, 704, 706, 711, 712, 714, 717, 721, 723, 724, 726, 727, 728, 729, 731, 737, 739, 740, 741, 742, 744, 746, 765, 767, 772, 773, 774, 775, 776, 780, 781, 785, 786, 787, 788, 790, 791, 792, 793, 795, 796, 797, 798, 805, 806, 807, 810, 813, 820, 821, 822, 824, 825, 827, 829, 830, 833, 834, 837, 838, 844, 853, 855, 873, 877, 878, 880, 882, 887, 888, 891, 894, 901, 903, 904, 905, 911, 929, 932, 933, 935, 938, 940, 948, 993, 996, 1006, 1018, 1026, 1028, 1035, 1048, 1053, 1054, 1055, 1056, 1068, 1070, 1071, 1072, 1073, 1075, 1076, 1081, 1763 and 1764

[0369] Compounds which manifested an inhibitory activity of 50% to 80% at a concentration of 10 µM:

15 Compd. Nos. 1, 2, 3, 4, 7, 13, 22, 23, 24, 25, 27, 31, 32, 38, 48, 83, 119, 121, 123, 131, 215, 216, 221, 235, 337, 351, 354, 358, 362, 363, 365, 367, 368, 369, 373, 378, 381, 384, 458, 459, 463, 465, 466, 467, 468, 478, 479, 480, 482, 485, 486, 487, 492, 493, 494, 495, 496, 498, 501, 503, 504, 507, 511, 512, 513, 520, 523, 527, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 545, 546, 547, 548, 549, 550, 551, 552, 558, 559, 560, 561, 562, 565, 567, 568, 569, 570, 572, 573, 574, 577, 581, 582, 594, 597, 599, 600, 602, 604, 606, 20 607, 608, 609, 613, 615, 616, 618, 619, 620, 621, 628, 630, 631, 632, 633, 634, 636, 637, 645, 651, 654, 655, 657, 661, 662, 664, 673, 674, 676, 678, 680, 683, 685, 687, 688, 689, 693, 703, 705, 707, 708, 709, 710, 713, 716, 718, 719, 720, 725, 730, 732, 733, 734, 735, 736, 749, 750, 751, 752, 753, 754, 756, 758, 760, 762, 763, 764, 766, 768, 769, 770, 771, 777, 778, 779, 784, 794, 799, 800, 802, 804, 808, 809, 811, 812, 815, 816, 819, 828, 831, 832, 835, 836, 839, 840, 845, 846, 847, 848, 850, 851, 854, 857, 858, 859, 860, 861, 862, 863, 865, 25 866, 867, 868, 872, 874, 876, 886, 899, 910, 942, 998, 1004, 1005, 1007, 1013, 1015, 1016, 1017, 1019, 1020, 1021, 1022, 1024, 1030, 1037, 1042, 1043, 1044, 1045, 1046, 1047, 1049, 1050, 1052, 1059, 1060, 1061, 1067, 1069, 1074, 1078, 1079, 1080 and 1766

[0370] Compounds which manifested an inhibitory activity of >80% at a concentration of 10 µM:

Compd. Nos. 461, 464, 469, 481, 490, 505, 509, 521, 526, 528, 544, 564, 566, 601, 605, 617, 622, 623, 627, 650, 656, 663, 668, 672, 686, 690, 692, 694, 715, 743, 747, 748, 755, 757, 759, 761, 782, 783, 803, 814, 817, 818, 826, 849, 856, 864, 869, 870, 871, 999, 1000, 1001, 1002, 1003, 1008, 1009, 1010, 1011, 1012, 1023, 1029, 1031, 1032, 1033, 1034, 1036, 1038, 1039, 1040, 1041, 1051, 1057, 1058, 1062, 1063, 1064, 1065, 1066, 1082 and 1083

[0371] Compounds which manifested an inhibitory activity of 20% to 50% at a concentration of 2μ M:

Compd. Nos. 1042, 1043, 1244, 1245, 1416, 1435, 1436, 1438, 1441, 1480, 1570, 1583, 1584, 1589, 1590, 1594, 1595, 1601, 1660, 1672, 1687, 1724, 1779, 1780, 1787, 1795, 1796, 1798, 1799, 1802, 1893, 1894, 1898, 1900, 1915, 1919, 1920, 2092, 2096, 2098 and 2100

[0372] Compounds which manifested an inhibitory activity of 50% to 80% at a concentration of 2 uM:

Compd. Nos. 1190, 1414, 1600, 2091, 2094 and 2095

[0373] Compounds which manifested an inhibitory activity of >80% at a concentration of 2 μM:

Compd. Nos. 2093, 2097, 2099, 2103 and 2104.

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- [Example 2044] Measurement of inhibitory activity against binding of MCP-1 to THP-1 cells
 - 1. Preparation of human MCP-1 gene-carrying recombinant baculovirus
- [0374] Two kinds of synthetic DNA primers (5'-CACTCTAGACTCCAGCATGA-3' and 5'-TAGCTGCAGATTCTT-GGGTTG-3') having restriction enzyme recognition sites applied on the basis of the known human MCP-1 gene sequence (see, for example, Yoshimura, T. et al. FEBS Letters 1989, 244, 487-493) were used to amplify a cDNA derived from human vascular endothelial cells (purchased from Kurabow) according to a PCR method. The amplified fragment was cleaved with restriction enzymes (Pstl and Xbal) and then ligated into a transfer vector pVL1393 (Invitrogen Co.).

The resulting vector was co-transfected with an infectious baculovirus into Sf-9 insect cells. Human MCP-1 gene recombinant baculoviruses were isolated from the obtained supernatant by a plaque assay method.

2. Synthesis of [125]-labeled human MCP-1 expressed with baculovirus

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[0375] According to the method of Ishii, K. et al. (see Biochemical and Biophysical Research Communications, 1995, 206, 955-961), 5×10^6 cells of Sf-9 insect cells were infected with 5×10^7 PFU (plaque-forming units) of the above human MCP-1 gene recombinant baculoviruses and cultured in EX-CELL 401 medium for 7 days. The resulting culture supernatant was affinity purified by a heparin-Sepharose column (Pharmacia Co.) and then subjected to reverse phase HPLC (Vydac C18 column) to afford a purified human MCP-1. The protein labeling of the resulting purified human MCP-1 was requested for Amersham Co. to obtain a [125 I]-labeled human MCP-1 expressed with baculovirus (specific activity: 2000 Ci/mmol) prepared by the Bolten Hunter method. The resulting [125 I]-labeled human MCP-1 was used for the following tests.

3-1. Measurement of inhibitory activity against binding of [125]-labeled human MCP-1 expressed with baculovirus to THP-1 cells (method 1)

[0376] THP-1 cells which are human monocytic leukemia cell line were suspended in an assay buffer [prepared by adding 0.1% of BSA and 25 mM of HEPES to RPMI-1640 (Gibco-BRL Co.) and adjusting the pH to 7.4] so as to provide $1. \times 10^7$ cells/mL to thereby afford a cell suspension. A solution obtained by diluting the test compound with the assay buffer was used as a test compound solution. A solution prepared by diluting the above [125 I]-labeled human MCP-1 expressed with baculovirus with the assay buffer so as to provide 1 μ Ci/mL was used as a lebeled ligand solution. In a 96-well filter plate (Millipore Co.), were aliquoted 25 μ L of the test compound solution, 25 μ L of the labeled ligand solution and 50 μ L of the cell suspension in the order mentioned for each well. The solutions were stirred (100 μ L of the reaction solution) and then incubated at 18 °C for 1 hour.

[0377] After completing the reaction, the reaction solution was filtered through a filter, and the filter was washed with 200 μ L of cold PBS twice (the reaction solution was filtered after adding 200 μ L of the cold PBS). The filter was airdried and 25 μ L of liquid scintillator was then added into each well to count the radioactivity retained by the cells on the filter using TopCount (Packard Instrument Co.).

[0378] The count when 100 ng of the above human MCP-1 expressed with baculovirus (unlabeled) instead of the test compound was added was subtracted as nonspecific adsorption, and the count when the test compound was not added was taken as 100%. Thereby, the inhibitory activity of the test compound against binding of the human MCP-1 to THP-1 cells was calculated.

Inhibition ratio (%) = $\{1-(A-B)/(C-B)\} \times 100$

(wherein A is the count when the test compound is added; B is the count when 100 ng of the unlabeled human MCP-1 is added; C is the count when only the [125]-labeled human MCP-1 is added).

[0379] When the inhibitory activity of the cyclic amine derivatives which are active ingredients of the present invention was measured, for example, the following compounds respectively manifested an inhibitory activity of 20 to 50%, 50% to 80% and >80% at a concentration of 1μ M, 10μ M or 100μ M.

[0380] Compounds which manifested an inhibitory activity of 20% to 50% at a concentration of 100 μM:

Compd. Nos. 3, 6, 11, 15, 16, 19, 28, 44, 88, 92, 94, 104, 111, 112, 124, 125, 133, 219, 220, 224, 228, 236, 338, 343, 346, 347, 348, 349, 362, 363, 367, 368, 371, 373, 381, 618, 847, 849, 850, 866, 867, 869, 870, 871, 872 and 873

[0381] Compounds which manifested an inhibitory activity of 50% to 80% at a concentration of 100 μ M:

Compd. Nos. 1, 8, 10, 12, 18, 21, 26, 30, 33, 35, 39, 84, 89, 90, 91, 96, 97, 98, 99, 100, 101, 103, 106, 108, 109, 110, 116, 122, 126, 216, 218, 221, 225, 226, 231, 330, 332, 333, 334, 337, 341, 342, 350, 352, 354, 356, 359, 360, 361, 364, 366, 374, 375, 379, 382, 462, 463, 464, 557, 686, 840, 841, 842, 843, 844, 845, 846, 848, 862, 863, 864, 865, 868

[0382] Compounds which manifested an inhibitory activity of >80% at a concentration of 100 μM:

Compd. Nos. 2, 4, 5, 7, 13, 14, 17, 20, 22, 23, 24, 25, 27, 29, 31, 32, 34, 36, 38, 40, 41, 42, 43, 45, 46, 47, 48, 49,

50, 83, 85, 86, 95, 102, 105, 107, 113, 114, 115, 119, 120, 121, 123, 127, 128, 129, 130, 131, 132, 134, 214, 215, 217, 227, 237, 238, 331, 335, 336, 339, 340, 345, 351, 355, 357, 358, 383, 458, 459, 460, 466, 558, 851, 852, 861 and 874

[0383] Compounds which manifested an inhibitory activity of 20% to 50% at a concentration of 10µM:

Compd. Nos. 12, 18, 30, 34, 40, 42, 43, 51, 52, 53, 54, 55, 56, 57, 59, 60, 64, 66, 75, 76, 77, 78, 79, 82, 89, 90, 97, 98, 102, 103, 116, 127, 128, 129, 130, 132, 135, 136, 140, 141, 144, 156, 157, 159, 160, 161, 162, 163, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 178, 179, 190, 191, 192, 195, 197, 200, 202, 203, 204, 205, 208, 233, 234, 235, 239, 240, 241, 242, 243, 245, 247, 249, 250, 255, 263, 264, 269, 274, 278, 279, 282, 306, 316, 317, 323, 324, 380, 404, 409, 433, 446, 448, 449, 451, 470, 471, 473, 476, 479, 486, 488, 489, 497, 498, 499, 501, 504, 507, 508, 509, 510, 512, 514, 516, 519, 527, 530, 532, 542, 545, 560, 563, 564, 565, 566, 568, 569, 572, 573, 574, 575, 578, 583, 584, 586, 587, 589, 590, 599, 600, 601, 603, 606, 612, 613, 620, 621, 622, 624, 625, 627, 629, 630, 632, 634, 636, 637, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 658, 678, 682, 687, 692, 694, 764, 775, 856, 857, 860, 881, 882, 883, 884, 890, 892, 899, 900, 903, 905, 907, 908, 911, 912, 916, 917, 921, 922, 923, 925, 927, 931, 932, 935, 939, 940, 968, 986, 1039, 1041, 1045, 1047, 1062, 1063 and 1083

[0384] Compounds which manifested an inhibitory activity of 50% to 80% at a concentration of 10 µM:

Compd. Nos. 7, 32, 36, 61, 62, 63, 65, 67, 69, 70, 71, 72, 73, 74, 81, 91, 105, 114, 121, 123, 134, 137, 138, 139, 146, 147, 148, 149, 151, 154, 165, 177, 232, 244, 248, 251, 252, 253, 256, 259, 261, 266, 267, 276, 286, 292, 293, 295, 301, 305, 307, 310, 314, 315, 320, 322, 328, 434, 435, 436, 437, 439, 440, 443, 447, 450, 452, 453, 454, 455, 456, 468, 469, 472, 474, 475, 477, 478, 480, 481, 482, 483, 485, 490, 493, 494, 500, 505, 511, 517, 520, 529, 534, 540, 543, 544, 548, 555, 556, 561, 562, 570, 576, 579, 611, 617, 853, 854, 855, 858, 859, 875, 877, 879, 880, 885, 886, 887, 888, 891, 894, 895, 904, 906, 909, 910, 913, 914, 918, 928, 930, 933, 937, 938, 945, 970, 1040, 1044 and 1046

[0385] Compounds which manifested an inhibitory activity of >80% at a concentration of 10 μM:

30 Compd. Nos. 31, 45, 46, 48, 58, 68, 80, 83, 113, 115, 142, 143, 145, 150, 152, 265, 268, 272, 275, 283, 285, 287, 288, 290, 291, 294, 296, 297, 302, 308, 309, 313, 321, 325, 326, 358, 438, 441, 442, 444, 445, 457, 466, 467, 484, 487, 491, 492, 495, 496, 503, 518, 537, 538, 547, 554, 876, 878, 919, 929 and 943

[0386] Compounds which manifested an inhibitory activity of 20% to 50% at a concentration of 1µM:

Compd. Nos. 1118, 1121, 1136, 1143, 1146, 1158, 1159, 1167, 1170, 1359, 1361, 1362 and 1363

[0387] Compounds which manifested an inhibitory activity of 50% to 80% at a concentration of 1µM:

Compd. Nos. 1133, 1134, 1137, 1141, 1156, 1161, 1162, 1163, 1164 and 1166

[0388] Compounds which manifested an inhibitory activity of >80% at a concentration of 1µM;

Compd. No. 1147.

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3-2. Measurement of inhibitory activity against binding of [125]-labeled human MCP-1 expressed with baculovirus to THP-1 cells (method 2)

[0389] THP-1 cells which are human monocytic leukemia cell line were suspended in an assay buffer (containing 50 mM of HEPES, 1.0mM of CaCl₂, 5.0 mM of MgCl₂ and 0.5% of BSA at pH 7.4) so as to provide 1 \times 10⁷ cells/mL to thereby obtain a cell suspension. A solution obtained by diluting the test compound with the assay buffer was used as a test compound solution. A solution prepared by diluting the above [125 I]-labeled human MCP-1 expressed with baculovirus with the assay buffer so as to provide 1 μ Ci/mL was used as a labeled ligand solution. In a 96-well filter plate (Millipore Co.), were aliquoted 25 μ L of the test compound solution, 25 μ L of the labeled ligand solution and 50 μ L of the cell suspension in the order mentioned for each well. The solutions were stirred (100 μ L of the reaction solution) and then incubated at 18 °C for 1 hour.

[0390] After completing the reaction, the reaction solution was filtered through a filter, and the filter was washed with 200 μ L of cold PBS twice (the reaction solution was filtered after adding 200 μ L of the cold PBS). The filter was air-

dried, and 25 µL of liquid scintillator was then added by into each well to count the radioactivity retained by the cells on the filter using TopCount (Packard Instrument Co.). The count when 100 ng of the above human MCP-1 expressed with baculovirus(unlabeled) instead of the test compound was added was subtracted as nonspecific adsorption, and the count when the test compound was not added was 100%. Thereby, the inhibitory activity of the test compound against binding of the human MCP-1 to THP-1 cells was calculated.

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Inhibition ratio (%) = \{1 - (A - B)/(C - B)\} \times 100
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(wherein A is the count when the test compound is added; B is the count when 100 ng of the unlabeled human MCP-1 is added; C is the count when only the [125]-labeled human MCP-1 is added).

[0391] When the inhibitory activity of the cyclic amine derivatives which are the active ingredients of the present invention was measured, for example, the following compounds respectively manifested an inhibitory activity of 20% to 50%, 50% to 80% and >80% at a concentration of $0.2 \,\mu\text{M}$, $1 \,\mu\text{M}$ or $10 \,\mu\text{M}$.

[0392] Compounds which manifested an inhibitory activity of 20% to 50% at a concentration of 10µM:

Compd. No. 1560

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[0393] Compounds which manifested an inhibitory activity of 50% to 80% at a concentration of 10µM:

Compd. No. 1550

[0394] Compounds which manifested an inhibitory activity of >80% at a concentration of 10 μM:

Compd. Nos. 541, 1042, 1043 and 1559

[0395] Compounds which manifested an inhibitory activity of 20% to 50% at a concentration of 1 μM:

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Compd. Nos. 1098, 1100, 1101, 1104, 1105, 1109, 1110, 1116, 1174, 1175, 1176, 1178, 1187, 1188, 1189, 1197, 1198, 1199, 1200, 1201, 1202, 1209, 1210, 1211, 1212, 1222, 1225, 1229, 1230, 1237, 1238, 1243, 1250, 1259, 1261, 1265, 1266, 1272, 1277, 1282, 1294, 1299, 1302, 1307, 1315, 1318, 1319, 1320, 1329, 1330, 1335, 1336, 1337, 1343, 1344, 1353, 1355, 1356, 1357, 1358, 1368, 1372, 1385, 1386, 1392, 1400, 1413, 1422, 1423, 1425, 1426, 1429, 1430, 1432, 1437, 1440, 1445, 1446, 1447, 1448, 1450, 1452, 1453, 1455, 1458, 1459, 1461, 1463, 1464, 1466, 1468, 1469, 1470, 1471, 1474, 1479, 1482, 1485, 1507, 1508, 1510, 1511, 1512, 1513, 1514, 1515, 1516, 1518, 1519, 1521, 1522, 1524, 1535, 1538, 1540, 1542, 1544, 1571, 1573, 1574, 1575, 1576, 1577, 1578, 1579, 1580, 1581, 1582, 1585, 1587, 1598, 1602, 1603, 1604, 1609, 1611, 1612, 1613, 1614, 1615, 1616, 1617, 1618, 1622, 1627, 1630, 1643, 1646, 1662, 1669, 1716, 1717, 1723, 1728, 1731, 1733, 1736, 1739, 1740, 1747, 1750, 1755, 1757, 1758, 1759, 1760, 1761, 1762, 1769, 1770, 1771, 1772, 1773, 1774, 1777, 1783, 1784, 1785, 1791, 1793, 1904, 1911, 1917, 2057, 2061, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2071, 2072, 2073, 2074, 2075, 2076, 2080, 2081, 2082, 2110, 2112, 2123, 2130, 2131, 2139, 2170, 2180, 2181, 2182, 2212, 2216, 2217, 2219, 2220, 2222, 2224, 2225, 2228, 2247, 2253, 2254, 2255, 2256, and 2257
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[0396] Compounds which manifested an inhibitory activity of 50% to 80% at a concentration of 1 μ M:

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Compd. Nos. 37, 298, 318, 1084, 1091, 1103, 1106, 1108, 1111, 1113, 1114, 1115, 1138, 1142, 1165, 1179, 1190, 1192, 1193, 1195, 1196, 1204, 1205, 1206, 1207, 1208, 1245, 1246, 1255, 1257, 1258, 1262, 1263, 1293, 1300, 1342, 1351, 1352, 1354, 1370, 1371, 1373, 1375, 1377, 1378, 1380, 1381, 1383, 1384, 1391, 1411, 1412, 1414, 1417, 1418, 1419, 1421, 1424, 1431, 1436, 1439, 1449, 1454, 1456, 1457, 1460, 1462, 1472, 1473, 1487, 1502, 1504, 1506, 1517, 1525, 1526, 1527, 1529, 1530, 1531, 1532, 1533, 1534, 1536, 1537, 1539, 1541, 1545, 1593, 1600, 1601, 1606, 1608, 1619, 1620, 1621, 1623, 1624, 1625, 1626, 1628, 1629, 1645, 1650, 1654, 1658, 1663, 1664, 1665, 1670, 1671, 1672, 1673, 1675, 1678, 1679, 1681, 1684, 1687, 1688, 1689, 1690, 1711, 1712, 1714, 1718, 1722, 1725, 1726, 1727, 1729, 1730, 1732, 1734, 1735, 1737, 1741, 1742, 1743, 1744, 1745, 1746, 1748, 1751, 1753, 1754, 1756, 1779, 1781, 1782, 1786, 1788, 1789, 1790, 1792, 1795, 1797, 1798, 1800, 1801, 1804, 1848, 1862, 1883, 1885, 1886, 1887, 1889, 1893, 1894, 1903, 1905, 1910, 1912, 1913, 1914, 1918, 1922, 1976, 1985, 2027, 2035, 2062, 2083, 2084, 2088, 2089, 2090, 2111, 2124, 2125, 2126, 2135, 2167, 2171, 2175, 2211, 2221, 2226, 2231 and 2240
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[0397] Compounds which manifested an inhibitory activity of >80% at a concentration of 1 μM:

Compd. Nos. 299, 311, 312, 329, 1042, 1043, 1085, 1119, 1191, 1203, 1220, 1228, 1236, 1244, 1256, 1288, 1295, 1308, 1310, 1376, 1382, 1393, 1395, 1415, 1416, 1420, 1435, 1438, 1441, 1480, 1481, 1570, 1583, 1584, 1589, 1590, 1594, 1595, 1607, 1634, 1660, 1661, 1666, 1668, 1695, 1696, 1697, 1698, 1699, 1701, 1702, 1703, 1704, 1705, 1706, 1707, 1708, 1709, 1713, 1724, 1749, 1752, 1775, 1776, 1778, 1780, 1787, 1794, 1796, 1799, 1802, 1803, 1841, 1869, 1870, 1871, 1872, 1876, 1877, 1892, 1896, 1897, 1898, 1899, 1900, 1901, 1902, 1906, 1907, 1908, 1909, 1915, 1916, 1919, 1920, 1921, 2085, 2086, 2087, 2113, 2114, 2118, 2119, 2120, 2121, 2122, 2127, 2128, 2129, 2132, 2133, 2136, 2137, 2138, 2159, 2161, 2162, 2169, 2172, 2178, 2179, 2187, 2189, 2193, 2210, 2213, 2214, 2215, 2218, 2227, 2229, 2230, 2232, 2233, 2235, 2236, 2237, 2238, 2241, 2242, 2243, 2244, 2245, 2246, 2248, 2249, 2250, 2251 and 2252

[0398] Compounds which manifested an inhibitory activity of 20% to 50% at a concentration of 0.2 µM:

Compd. Nos. 1680, 1682, 1686, 1691, 1694, 1700, 1805, 1810, 1811, 1812, 1813, 1815, 1816, 1817, 1818, 1819, 1820, 1824, 1825, 1826, 1827, 1828, 1832, 1833, 1834, 1835, 1836, 1839, 1840, 1842, 1843, 1851, 1852, 1853, 1854, 1855, 1856, 1858, 1859, 1860, 1863, 1864, 1865, 1866, 1868, 1874, 1878, 1879, 1880, 1888, 1890, 1891, 1895, 1926, 1927, 1928, 1929, 1930, 1934, 1935, 1937, 1945, 1946, 1951, 1952, 1953, 1954, 1959, 1960, 1961, 1962, 1966, 1969, 1970, 1971, 1972, 1973, 1977, 1978, 1979, 1980, 1981, 1985, 2014, 2027, 2028, 2033, 2035, 2039, 2040, 2041, 2042, 2044, 2045 and 2046

[0399] Compounds which manifested an inhibitory activity of 50% to 80% at a concentration of 0.2 μM:

Compd. Nos. 1677, 1678, 1679, 1681, 1687, 1688, 1689, 1690, 1695, 1697, 1808, 1809, 1841, 1848, 1861, 1862, 1869, 1870, 1871, 1872, 1873, 1876, 1877, 1883, 1884, 1885, 1886, 1887, 1889, 1893, 1894 and 1976

25 [0400] Compounds which manifested an inhibitory activity of >80% at a concentration of 0.2 μ M:

Compd. Nos. 1696 and 1892.

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[Example 2045] Measurement of inhibitory activity against binding of MCP-1 to cells expressing the MCP-1 receptor (Evaluation using [1251]-labeled human MCP-1)

1. Obtaining of cells expressing the MCP-1 receptor

[0401] An MCP-1 receptor cDNA fragment obtained by Yamagami, S. et al. (see Biochemical and Biophysical Research Communications, 1994, 202, 1156-1162) was cloned into an Notl site of an expression plasmid pCEP-4 (Invitrogen Co.), and the resulting plasmid was transfected into human kidney epithelial cell line 293-EBNA with a Lipofectamine reagent (Gibco-BRL Co.) and the cells were cultured in the presence of a selective agent (Hygromycin) to provide a stably expressing transfactant line. The expression of the receptor was confirmed by binding properties of the [1251]-labeled human MCP-1.

2. Measurement of inhibitory activity against binding of [1251]-labeled human MCP-1 expressed with baculovirus to MCP-1 receptor-expressing cells

[0402] The MCP-1 receptor-expressing cells on a tissue culture dish were scraped using a cell scraper and suspended in the assay buffer [prepared by adding 0.1% of BSA and 25 mM of HEPES to D-MEM (Gibco-BRL Co.) and adjusting the pH to 7.4] to thereby provide a cell suspension of a concentration 6×10^6 cells/ml. The same subsequent procedures were performed as described in Example 2044.

[0403] When the inhibitory activity of the cyclic amine derivatives, which were the active ingredients of the present invention, was measured, the inhibitory activity of the representative compounds in the Example was approximately the same as that described in Example 2044.

[Example 2046] Measurement of inhibitory activity against cell chemotaxis

[0404] In order to determine the inhibitory activity of the compounds according to the present invention against the cell chemotaxis, human monocytic leukemia cell line THP-1 were used as chemotactic cells according to the method of Fall et al. (J. Immunol. Methods, 1980, 33, 239-247) to determine the cell chmotaxis caused by monocyte chemotactic factor MCP-1 as follows: Namely, 2×10^6 cells/mL of the THP-1 cells [suspended in RPMI-1640 (Flow Laboratories Co.) + 10% FCS] were placed in the upper chamber (200 μ L) of a 96-well microchemotaxis chamber (Neuroprobe ®),

and human recombinant MCP-1 (Peprotech Co.) diluted with the same solution so as to provide the final concentration of 20 ng/mL was placed in the lower chamber (35 μ L). A polycarbonate filter (PVP-free, Neuroprobe ®) was placed between the two chambers. These were incubated in the presence of 5% of CO₂ at 37°C for 2 hours.

[0405] The filter was removed, and the cells which had migrated to the undersurface of the filter were immobilized, stained using Diff Quick (Kokusai Shiyaku Co.) and then measured at a measuring wavelength of 550 nm using a plate reader (Molecular Device Co.) to determine the means of 3 wells. Thereby, the indication of the number of cells migrated was obtained. The test compound together with the THP-1 cells was added to the upper chamber at various concentrations to determine the inhibitory activity against cell chemotaxis [degree of inhibition: IC_{50} (μ M)]. The degree of inhibition was defined as {(number of cells migrated with MCP-1 when no test compound was added to the upper chamber) - (number of cells migrated when no MCP-1 was added to the lower chamber) = 100%}, and the concentration of the compound manifested 50% of the inhibition was designated as IC_{50} .

[0406] When the inhibitory activity of the cyclic amine derivatives which are the active ingredients of the present invention was determined, for example, the IC_{50} value of the following compounds was 0.1 μ M or below.

[0407] Examples of compounds which manifested an IC₅₀ value of 0.1 μ M or below:

Compd. Nos. 4, 37, 298, 299, 311, 312, 318, 329, 461, 886, 909, 1042, 1043, 1085, 1119, 1138, 1142, 1165, 1179, 1191, 1203, 1205, 1220, 1228, 1236, 1244, 1245, 1256, 1288, 1293, 1295, 1308, 1310, 1352, 1376, 1382, 1393, 1395, 1416, 1420, 1435, 1436, 1438, 1441, 1480, 1531, 1532, 1570, 1583, 1584, 1589, 1590, 1594, 1595, 1600, 1601, 1607, 1660, 1661, 1664, 1666, 1668, 1698, 1699, 1701, 1702, 1703, 1704, 1706, 1707, 1708, 1709, 1713, 1775, 1776, 1778, 1779, 1787, 1794, 1796, 1799, 1802, 1803, 1896, 1898, 1899, 1900, 1901, 1902, 1906, 1907, 1908, 1909, 1915, 1916, 1919, 1920, 1921, 2087, 2114, 2128, 2129, 2132, 2137, 2141, 2144, 2157, 2158, 2189, 2213, 2214, 2235, 2236, 2241, 2242, 2244, 2249, 2250 and 2251.

[0408] The results in Examples 2043; 2044. 2045 and 2046 definitely show that the compounds of the present invention as a receptor antagonist of chemokines such as MIP-1α and/or MCP-1 have the inhibitory activity against actions of the chemokines on target cells.

[Example 2047] Studies on inhibitory effects on collagen-induced arthritis in mice

[0409] Collagen-induced arthritis in mice was induced according to the method of Kato et al. (Arthritis in mice induced by a single immunization with collagen, Ann. Rheum. Dis., 55, 535-539, 1996).

1. Method

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- [0410] Type II collagen derived from a bovine joint (Collagen Gijutsukenshukai) was emulsified with an volume of a Freund's complete adjuvant (ICN Immunobiologicals) to prepare a homogeneous emulsion. An ultrasonic homogenizer (Taitec) was used to prepare the emulsion. The emulsion (in a dose of 0.15 mg/0.1 mL/body) was intracutaniously injected into the base of the tail of DBA/1 mice (Charles River, Japan Inc.) by using a glass syringe for tuberculin and a 27G injection needle.
- 40 [0411] The test compound was suspended in a 0.5% aqueous solution of sodium carboxymethyl cellulose (CMC, Wako Pure Chemical Industries, Ltd.) with a mortar to prepare a prescribed administration suspension, which was orally administered from the date after the administration of the emulsion.
 - [0412] The experimental groups are three of a group administered with 0.5% of CMC (hereinafter referred to as the control group) and groups administered with 30 mg/kg or 100 mg/kg of the test compound. The solution or the test compound was administered once a day, and the number of animals in each group was 16.

2. Evaluation of arthritis

[0413] The degree of joint swelling was scored for each digital joint of four limbs after the passage of 12 weeks from the administration of the emulsion according to the method of Abe (immunotherapy in arthritis model, Japanese Jonrral of Inflammations 12, 417-422, 1992). Each limb was scored in four grades of scores 0 to 3, and the maximum was score 12.

3. Actions on synovial hyperplasia, chondrolysis of articular cartilages and osteolysis of subchondral bone

[0414] After observing the arthritis scores, the right hindlimbs were removed. After embedding in paraffin, thin slice of knee joint were prepared and subjected to hematoxylin-eosin staining to evaluate actions on synovial hyperplasia, chondrolysis, destruction of articular cartilages and osteolysis of subchondral bone according to a conventional method.

The rating was carried out in five grades of scores 0 to 4 for each measurement item.

4. Results of evaluation

[0415] The category type Dunnett's tests compared with the control group were carried out, and a p value of 0.05 or below was taken as significantly different. The following graphs are expressed as mean ± standard deviation (SD). Fig. 1 illustrates the results of arthritis when Compd. No. 1583 was orally administered for 12 weeks. The group administered with Compd. No. 1583 significantly inhibited arthritis scores as compared with the control group.

[0416] Figs. 2 to 4 respectively illustrates results of Compd. No.1583 on synovial hyperplasia, chondrolysis of articular cartilages and osteolysis of subchondral bone. Compd. No.1583 significantly inhibited for all the evaluation items.

[Example 2048] Studies on inhibitory effects on collagen-induced arthritis in rats

[0417] Collagen-induced arthritis in rats was induced by modifying the method of Trentham et al. (Autoimmunity to type II collagen: an experimental model of arthritis. J. Exp. Med., 146, 857-68 (1977) as follows:

1. Method

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[0418] Type II collagen derived from a bovine joint (Collagen Gijutsukenshukai) and muramyl dipeptide (CHEMICON International) were mixed with an Freund's incomplete adjuvant so as to provide each final concentration of 0.08% and 0.02% to thereby prepare a homogenous emulsion. The resulting emulsion was prepared by vigorous stirring at 4 °C in two glass syringes connected with a connector. One mL of the emulsion was injected intradermally in 10 sites on the back of Lewis female rats (Charles River Japan, Inc., 6-weeksold) by using a glass syringe for tuberculin and a 26G injection needle. After one week, the base of the tail was additionally immunized (boosted) intradermally with 0.1 mL of the emulsion prepared by the same method as described above.

[0419] The test compound was suspended in a 0.5 % aqueous solution of sodium carboxymethylcellulose (CMC, Wako Pure Chemical Industries, Ltd.) with a mortar to prepare a prescribed administration suspension, which was orally administered every day for 3 weeks after the date of the initial administration of the emulsion.

[0420] The experimental groups were a group of no treatment (intact group), a group administered with 0.5% of the CMC (hereinafter referred to as the control group) and a group administered with 300 mg/kg of Compd. No. 1245. The solution or the test compound was administered once a day. The number of animals in each group was 8.

2. Evaluation of arthritis

[0421] The limb joint swelling of hindlimbs was evaluated by determining a change in the volume of the limb joints. The footpad volumes of the right and left hindlimbs of rats were measured total 7 times of the date of boosting, 2, 5, 7, 9, 12 and 14 days after the date of boosting by using a rat hindlimb footpad volume meter (TK-105, UNICON). The obtained results were expressed as an increasing rate after the date of boosting by taking the footpad volume on the date of boosting as 100%. The mean of the group was obtained as the mean of all the left and right hindlimb volumes in each group.

3. Results of evaluation

[0422] Fig. 5 illustrates results of arthritis when Compd. No. 1245 was orally administered every day for 3 weeks. Values in the figure are expressed as mean ±S.E. Student's t-tests or Wilcoxon tests were carried out comparing with the control group, and a P value of 0.05 or below was taken as significantly different. The group administered with Compd. No. 1245 significantly inhibited joint swelling (after 5, 7 and 14 days: P<0.01 and after 9 and 12 days: P<0.001) as compared with the control group at each time point of 5, 7, 9, 12 and 14 days after the boosting.

[0423] The results of Examples 2047 and 2048 show that the compounds of the present invention have effective remedial or prophylactic effects on diseases in association with chondrolysis of cartilage or osteolysis such as arthritis, rheumatoid arthritis, osteoarthritis, traumatic articular destruction, osteoporosis or tumor.

[Example 2049] Studies on inhibitory actions in Masugi's nephritis model in WKY-rats

1. Method (common to Experiments 1 and 2)

[0424] Rabbits were immunized with a trypsin fraction of rat kidney cortex to provide an anti-glomerular basement membrane serum which was intravenously injected to 4-weeks-old female WKY rats (Charles River) in a dose of 2.5

mL/kg body weight to induce glomerulonephritis.

[0425] After injection of the antiserum, urine of each animal was collected for 24 hours with metabolic cages for rats (Clea Japan, Inc.) on the 1st, 4th, 7th, 10th and 14th days after the injection. The amount of the urine was measured by urine weight and the protein content in the urine was measured by using a kit for assaying proteins in urine and cerebrospinal fluid (Tonein TP-II, Otsuka Pharmaceutical Co., Ltd.) to determine the amount of proteins excreted in urine per day.

[0426] Serum of the animals subjected to the experiments was collected on the 15th day after injecting the antiserum, and creatinine concentration in blood was measured with a creatinine assay kit (Autosera ®, Daiichi Pure Chemicals Co., Ltd.) using a Hitachi 7070 model autoanalyzer.

[0427] The test compound was daily orally administered in a dose of 100 mg/kg body weight twice a day from the date of injecting the anti-glomerular basement membrane serum (about 10:00 a.m. and about 6:00p.m. in Experiment 1 and about 10:00 a.m. and about 5:00 p.m. in Experiment 2). In the control group, only the solution (a 0.5% aqueous solution of sodium carboxymethylcellulose) was orally administered. The administration volume was 10 mL/kg body weight, and the number of animals (N) was 10.

2. Results and Discussion

[0428] The detection of proteinuria began in each experimental group on the 4th day after injecting the anti-glomerular basement membrane serum, and the concentration of the urinary proteins was subsequently increased to the 14th day with time to induce nephritis. In the group administered with Compd. No. 1583, a tendency to inhibit the concentration of urinary proteins by 26% was found as compared with the control group on the 7th day after injecting the antiserum. A significant inhibition of the concentration of urinary proteins was found by 51 and 54% on the 10th and 14th days (p<0.01, Mann-Whitney U test). (Fig. 6). When the creatinine concentration in blood was measured on the 15th day after injecting the anti-glomerular basement membrane serum, a significant decrease of 20% (p<0.01, Mann-Whitney U test) was found in the group administered with Compd. No. 1583 as compared with the control group (Table 53). [0429] Therefore, it is found that the glomerular injury and renal function exacerbation of rats were alleviated with Compd. No. 1583 to inhibit nephritis.

Table 53

Inhibitory Effects on Serum Creatinine Serum Creatinine Concentration (mg/dl) on the 15th Day of Administering Compound		
Placebo	Compd. No. 1583	
0.49±0.06	0.39±0.03**	

2-2. Experiment 2

[0430] The detection of proteinuria began in each experimental group on about the 4th day after injecting the antiglomerular basement membrane serum, and the concentration of the urinary proteins was subsequently increased to the 14th day with time to confirm the induction of nephritis. In the group administered with Compd. No.1245, a significant (p<0.001, Mann-Whitney U test) inhibition of the concentration of urinary proteins was respectively found by 74, 85, 81 and 82% on the 4th, 7th, 10th and 14th days after injecting the antiserum as compared with the control group (Fig. 7). When the creatinine concentration in blood was measured on the 15th day after injecting the anti-glomerular basement membrane serum, a significant decrease of 10% (p<0.05, Student's t-test) was found in the group administered with compound 1245 as compared with the control group (Table 54).

[0431] Therefore, it is found that the glomular injury and renal function exacerbation of rats were alleviated with Compd. No.1245 to inhibit nephritis.

Table 54

Inhibitory Effects on Serum Creatinine				
Serum Creatinine Concentration (mg/dl) on the 15th Day of Administering Compd. No. 1245				
Control	Compd. No. 1245			
0.53±0.05	0.48±0.04‡			

[0432] The above results show that the compound of the present invention has effective remedial or prophylactic effects on nephritis or nephropathy such as glomerulonephritis, interstitial nephritis or nephrotic syndrome.

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[Example 2050] Studies on inhibitory effects in chronic relapsing experimental allergic encephalomyelitis in mice

1. Method

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[0433] Animal models of chronic recurrent experimental allergic encephalomyelitis were prepared according to the method described in the report by Okuda et al. [Okuda Y., et al. J. Neuroimmunol. 81, 201-210 (1998)].

[0434] Into the abdomen of 8-weeks-old female SJL/J \times PL/J F1 mice (Jackson Lab.), were subcutaneously injected 100 μ L of an emulsion of an Freund's incomplete adjuvant (Diffco) containing 500 μ g of rabbit myelin basic protein (Sigma) and 500 μ g of Mycobacterium tuberculosis H37Ra (Difco)/isotonic sodium chloride solution = 1:1 (volume ratio). After 24 hours, 100 μ L of isotonic sodium chloride solution containing 400 ng of Bordetella pertussis toxin (Sigma) was intraperitoneally injected to induce the chronic relapsing experimental allergic encephalomyelitis. The number of animals in each group was 10.

[0435] The test compound was suspended in a 0.5% (weight/volume) aqueous solution of sodium carboxymethyl-cellulose (Wako Pure Chemical Industries, Ltd.) with a mortar to prepare a prescribed suspension, which was orally administered from the date of injection of the emulsion.

[0436] Clinical symptoms of the chronic relapsing experimental allergic encephalomyelitis were evaluated by observation on animal individuals once a day by using the method described by Tahira et al. ["Methods of Immunological Experimental Procedures" p. 1178-1181, Nankodo (1995)]. Namely, score 0 = normal; score 1 = limp tail; score 2 = slight walking abnormality; sore 3 = apparent hindlimb paresis; score 4 = complete hindlimb paralysis and score 5 = moribund or death.

2. Results and Discussion

2-1. Experiment 1: Effects of Compd. No. 1583

[0437] Table 55 and Fig. 8 show the results to 41 days after injection of the emulsion.

[0438] The change in symptoms was expressed by means of the respective experimental groups on each observation day. In the maximal clinical scores in Table 55, the maximal value of the clinical scores shown in the observation period by the respective animals were adopted as the representative scores of the example. As to statistical analytical methods, nonparametric tests among some groups without comparison with to the control group were used for clinical scores and multiple comparisons with the control group (Dunnett's multiple comparison) were used for other evaluation items

[0439] A tendency to delay the onset date (no significant difference), symptom inhibition (p<0.05) and shortening of onset period (p<0.05) were found at the first attack in the group administered with 100 mg/kg body weight of Compd. No.1583 as compared with the control group. In the group administered with 30 mg/kg body weight of Compd. No. 1583, distinct effects on the items were not found; however, the tendency of dose-dependent effects was found. In Fig. 8, "compound 1" is not Compd. No. 1 in the present invention, but means the compound of Compd. No. 1583.

Table 55

		Table 55	
Experimental Group	Control Group	Compd. No. 1583 30 mg/kg body weight	Compd. No. 1583 100 mg/kg body weight
First Attack			
Onset Date	12.6±1.9	12.3 ±1.9	13.6±2.0
Maximal Clinical Score	3.9±0.6	3.5±0.9	2.4±1.3*
Duration of Clinical Sign	8.8±2.5	9.8±3.3	5.7±3.8*
Second Attack (Relapse)			
Onset Date	26.8±7.5	26.3±3.4	28.5±4.7*
Maximal Clinical Score	3.8±0.8	3.7±0.6	3.0±0.9*
Duration of Clinical Sign	Not calculated	Not calculated	Not calculated
Note: *: p<0.05	•		1

2-2. Experiment 2: Effects of Compd. No. 1245

[0440] Table 56 and Fig. 9 illustrate the results to 21 days after injection of the emulsion.

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[0441] The change in symptoms was expressed as means of the respective experimental groups on each observation day. As to the maximal clinical scores in Table 56, the maximal values of clinical scores manifested by the respective animals during the observation period were adopted as representative scores of the example. As to statistical analytical methods, nonparametric tests between two groups without comparison with to the control group were used for clinical scores and two group comparison with the control group (Student's t-tests) was used for the other evaluation items.

[0442] The delay in onset date (p<0.05) and a tendency to inhibit symptoms (no significant difference) were found in the group administered with 300 mg/kg body weight of Compd. No. 1245 as compared with the control group.

Table 56

Experimental Group	Control Group	Compd. No. 1245 300 mg/kg body weight
Incidence (Number of Onset Animals/Number of Immunized Animals)	34/39	17/19
Onset Date	11.2±2.0	13.2±2.4*
Maximal Clinical Score	3.0±0.9	2.5±1.5
Duration of Clinical Sign	5.5±1.7	5.4±2.4

^{*}p < 0.05

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[0443] The above results show that the compound of the present invention has effective remedial or prophylactic effects on demyelinating diseases such as multiple sclerosis.

[0444] The results shown in Examples 2043 to 2050 reveal that the compound of the present invention as a chemokine receptor antagonist can be useful as remedies or prophylactics for various diseases considered to be associated with chemokines such as MIP-1α and/or MCP-1 such as atherosclerosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, nephritis (nephropathy), multiple sclerosis, pulmonary fibrosis, cardiomyopathy, hepatitis, pancreatitis, sarcoidosis, Crohn's disease, endometriosis, congestive heart failure, viral meningitis, cerebral infarction, neuropathy, Kawasaki disease, sepsis, allergic rhinitis and allergic dermatitis.

[Example 2051] Production of Tablets

[0445] A tablet containing 30 mg of Compd. No. 1583 was prepared according to the following prescription:

Compd. No. 1583	30 mg
Lactose ·	87 mg
Starch	30 mg
Magnesium stearate	3 mg

[Example 2052] Production of Parenteral Injection

[0446] Solutions for injection containing 0.3 mg of hydrochloride of Compd. No. 1583 in 1 mL were prepared according to the following prescription:

Compd. No. 1583 (hydrochloride)	⁻ 30 mg
Sodium chloride	900 mg
Distilled water for injection	100 mL

Industrial Applicability

[0447] Cyclic amine compounds used in the present invention, pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable C_1 - C_6 alkyl addition salts thereof as a chemokine receptor antagonist have inhibitory activities on actions of chemokines such as MIP-1 α and/or MCP-1 on target cells. Therefore, the cyclic amine compounds, pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable C_1 - C_6 alkyl addition salts thereof are useful as remedies and/or prophylactics for diseases such as atherosclerosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, nephritis (nephropathy), multiple sclerosis, pulmonary fibrosis, cardiomyopathy, hepatitis, pancreatitis, sarcoidosis, Crohn's disease, endometriosis, congestive heart failure, viral meningitis, cerebral infarction, neuropathy, Kawasaki disease, sepsis, allergic rhinitis and allergic dermatitis wherein infiltration of leuko-

cytes such as monocytes or lymphocytes into tissues plays a principal role in progression and maintenance of diseases.

Claims

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Remedies or prophylactics for diseases in association with chemokines or chemokine receptors comprising compounds represented by the following formula (I), pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable C₁-C₆ alkyl addition salts thereof as an active ingredient,

wherein

R1 is a phenyl group, a C3-C8 cycloalkyl group or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms; the phenyl group or the aromatic heterocyclic group in the above R1 may be condensed with a benzene ring or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms to form a condensed ring; the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring in the above R¹ may be substituted with an optional number of halogen atoms, hydroxy groups, cyano groups, nitro groups, carboxy groups, carbamoyl groups, C₁-C₆ alkyl groups, C₃-C₈ cycloalkyl groups, C₂-C₆ alkenyl groups, C₁-C₆ alkoxy groups, C₁-C₆ alkylthio groups, C₃-C₅ alkylene groups, C₂-C₄ alkylenoxy groups, C₁-C₃ alkylenedioxy groups, phenyl groups, phenoxy groups, phenylthio groups, benzyl groups, benzyloxy groups, benzoylamino groups, C_2-C_7 alkanoyl groups, C_2-C_7 alkoxycarbonyl groups, C_2-C_7 alkanoyloxy groups, C_2-C_7 alkanoylamino groups, C2-C7 N-alkylcarbamoyl groups, C4-C9 N-cycloalkylcarbamoyl groups, C1-C6 alkylsulfonyl groups, C3-C8 (alkoxycarbonyl)methyl groups, N-phenylcarbamoyl groups, piperidinocarbonyl groups, morpholinocarbonyl groups, 1-pyrrolidinylcarbonyl groups, bivalent groups represented by the formula;-NH(C=O)O-, bivalent groups represented by the formula: -NH(C=S)O-, amino groups, mono(C₁-C₆ alkyl)amino groups or di(C₁-C₆ alkyl)amino groups; the substitutens of the phenyl group, the C₃-C₈ cycloalkyl group, the aromatic heterocyclic group or the condensed ring may further be substituted with an optional number of halogen atoms, hydroxy groups, amino groups, trifluoromethyl groups, C_1 - C_6 alkyl groups or C_1 - C_6 alkoxy groups;

 R^2 is a hydrogen atom, a C_1 - C_6 alkyl group, a C_2 - C_7 alkoxycarbonyl group, a hydroxy group or a phenyl group; the C_1 - C_6 alkyl group or the phenyl group in the R^2 may be substituted with an optional number of halogen atoms, hydroxy groups, C_1 - C_6 alkyl groups or C_1 - C_6 alkoxy groups, with the proviso that R^2 is not a hydroxy group when j is 0;

j is an integer of 0 to 2;

k is an integer of 0 to 2;

m is an integer of 2 to 4;

n is 0 or 1;

 R^3 is a hydrogen atoms or a C_1 - C_6 alkyl group which may be substituted with (one or two phenyl groups which may respectively be substituted with an optional number of the same or different halogen atoms, hydroxy groups, C_1 - C_6 alkyl groups or C_1 - C_6 alkoxy groups);

 R^4 and R^5 are the same or different and are each a hydrogen atom, a hydroxy group, a phenyl group or a C_1 - C_6 alkyl group; the C_1 - C_6 alkyl group in the R^4 and R^5 may be substituted with an optional number of halogen atoms, hydroxy groups, cyano groups, nitro groups, carboxy groups, carbamoyl groups, mercapto groups, guanidino groups, C_3 - C_8 cycloalkyl groups, C_1 - C_6 alkoxy groups, C_1 - C_6 alkylthio groups, (phenyl groups which may be substituted with an optional number of halogen atoms, hydroxy groups, C_1 - C_6 alkyl groups, C_1 - C_6 alkoxy groups or benzyloxy groups), phenoxy groups, benzyloxy groups, benzyloxycarbonyl groups, C_2 - C_7 alkanoyl groups, C_2 - C_7 alkyl groups, C

p is 0 or 1; q is 0 or 1;

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G is a group represented by -CO-, -SO₂-, -CO-O-, -NR⁷-CO-, -CO-NR⁷-,-NH-CO-NH-, -NH-CS-NH-, -NR⁷-SO₂-, -SO₂-NR⁷-, -NH-CO-O- or -O-CO-NH-, wherein R⁷ is a hydrogen atom or a C₁-C₆ alkyl group or R⁷, together with R⁵, may form a C₂-C₅ alkylene group;

R⁶ is a phenyl group, a C₃-C₈ cycloalkyl group, a C₃-C₆ cycloalkenyl group, a benzyl group or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms; the phenyl group, the benzyl group or the aromatic heterocyclic group in the R⁶ may be condensed with a benzene ring or an aromatic heterocyclic group having 1 to 3 oxygen atoms, sulfur atoms and/or nitrogen atoms as heteroatoms to form a condensed ring; the phenyl group, the C_3 - C_8 cycloalkyl group, the C_3 - C_6 cycloalkenyl group, the benzyl group, the aromatic heterocyclic group or the condensed ring in the above R⁶ may further be substituted with an optional number of halogen atoms, hydroxy groups, mercapto groups, cyano groups, nitro groups, thiocyanato groups, carboxy groups, carbamoyl groups, trifluoromethyl groups, C1-C6 alkyl groups, C₃-C₈ cycloalkyl groups, C₂-C₆ alkenyl groups, C₁-C₆ alkoxyl groups, C₃-C₈ cycloalkyloxy groups, C₁-C₆ alkylthio groups, C₁-C₃ alkylenedioxy groups, phenyl groups, phenoxy groups, phenylamino groups, benzyl groups, benzoyl groups, phenylsulfinyl groups, phenylsulfonyl groups, 3-phenylureido groups, C2-C7 alkanoyl groups, C_2 - C_7 alkoxycarbonyl groups, C_2 - C_7 alkanoyloxy groups, C_2 - C_7 alkanoylamino groups, C_2 - C_7 N-alkylcarbamoyl groups, C_1 - C_6 alkylsulfonyl groups, phenylcarbamoyl groups, N,N-di $(C_1$ - C_6 alkyl)sulfamoyl groups, amino groups, mono(C₁-C₆ alkyl)amino groups, di(C₁-C₆ alkyl)amino groups, benzylamino groups, C₂-C₇ (alkoxycarbonyl)amino groups, C₁-C₆ (alkylsulfonyl)amino groups or bis(C₁-C₆ alkylsulfonyl)amino groups; the substitutents of the phenyl group, the C₃-C₈ cycloalkyl group, the C₃-C₈ cycloalkenyl group, the benzyl group, the aromatic heterocyclic group or the condensed ring may further be substituted with an optional number of halogen atoms, cyano groups, hydroxy groups, amino groups, trifluoromethyl groups, C₁-C₆ alkyl

C₁-C₆ alkoxyl groups, C₁-C₆ alkylthio groups, mono(C₁-C₆ alkyl)amino groups or di(C₁-C₆ alkyl)amino groups.

- 2. The remedies or prophylactics according to claim 1, wherein the diseases are associated with chondrolysis of cartilage or osteolysis.
- 30 3. The remedies or prophylactics according to claim 2, wherein the diseases associated with the chondrolysis of cartilage or osteolysis are arthritis, rheumatoid arthritis, osteoarthritis, trauma, osteoporosis or tumor.
 - 4. The remedies or prophylactics according to claim 1, wherein the diseases are rheumatoid arthritis.
- 35 5. The remedies or prophylactics according to claim 1, wherein the diseases are nephritis or nephropathy.
 - **6.** The remedies or prophylactics according to claim 5, wherein the diseases are glomerulonephritis, interstitial nephritis or nephrotic syndrome.
- The remedies or prophylactics according to claim 1, wherein the diseases are demyelinating diseases.
 - 8. The remedies or prophylactics according to claim 7, wherein the diseases are multiple sclerosis.
 - 9. The remedies or prophylactics according to claim 1, wherein chemokines are MIP-1 α or MCP-1.
 - 10. The remedies or prophylactics according to claim 1, wherein chemokine receptors are CCR1 or CCR2.
 - 11. A pharmaceutical composition comprising the compounds represented by the above formula (I), pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable C₁-C₆ alkyl addition salts thereof as an active ingredient.

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Fig. 1

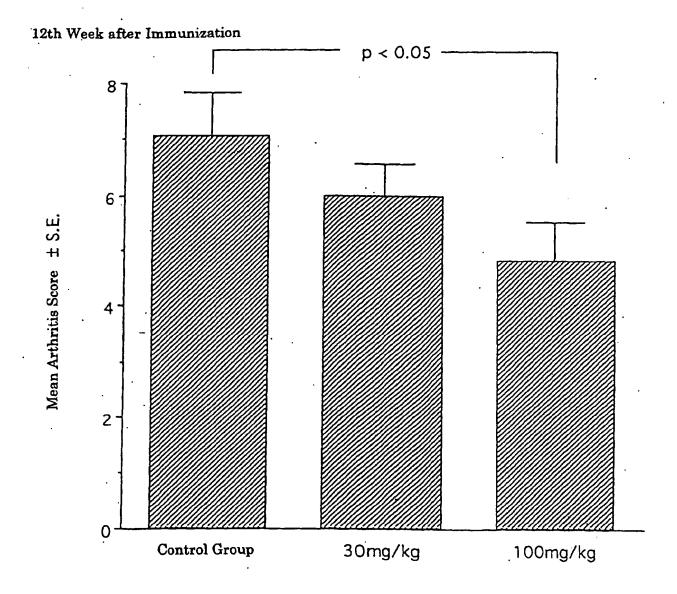


Fig. 2

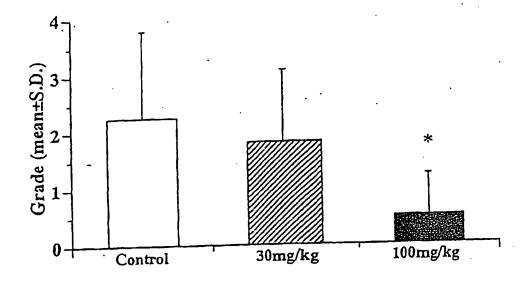


Fig. 3

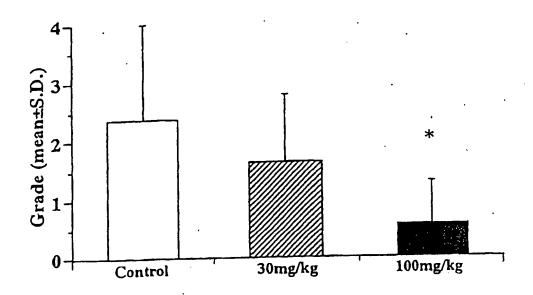


Fig. 4

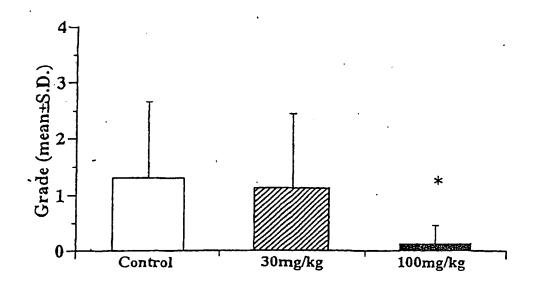
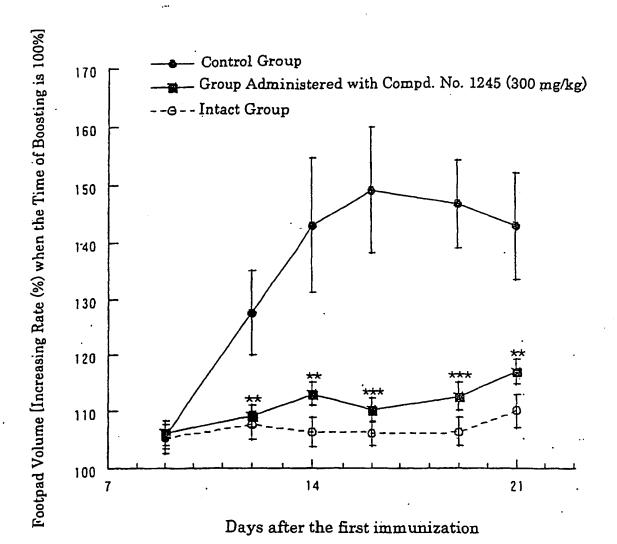


Fig. 5





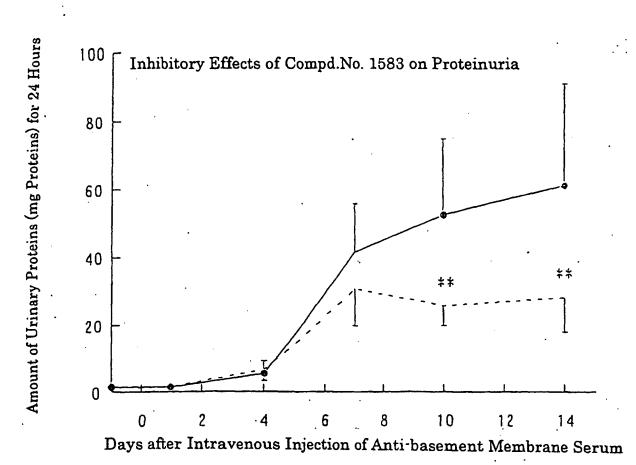
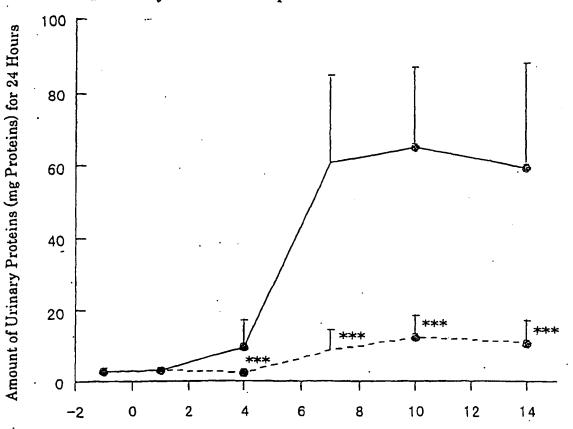
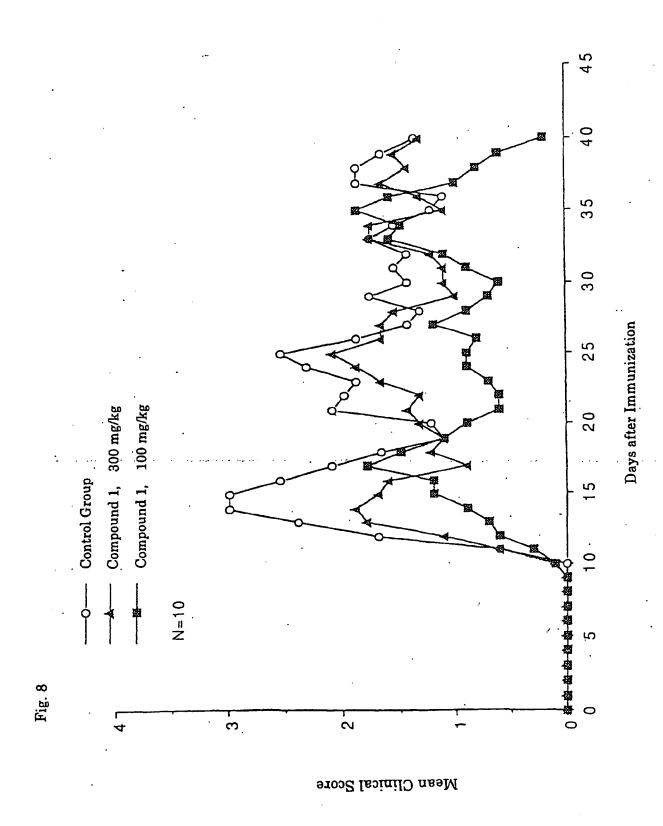


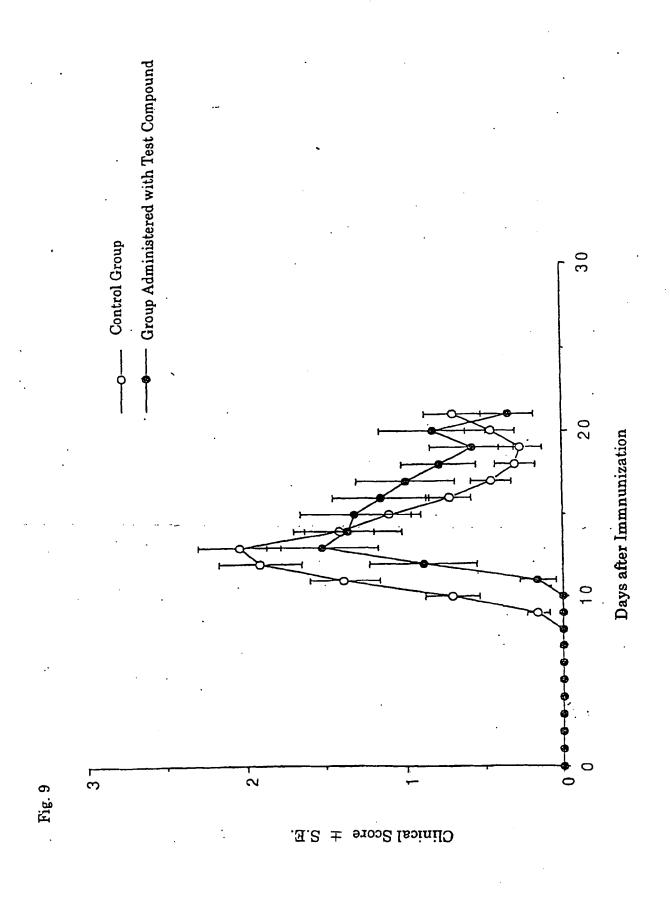
Fig. 7

Inhibitory Effects of Compd. No. 1245 on Proteinuria



Days after Intravenous Injection of Anti-basement Membrane Serum





INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP00/03203

Int.(4709 // C	SIFICATION OF SUBJECT MATTER C1	55, A61P43/00, 29/00, 9/00, 3 1/06, 12, 14, 409/06, 12, 14,	7/00, 25/00, 11/00
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Documentat	ion searched other than minimum documentation to the	e extent that such documents are included	
	ata base consulted during the international search (nam. STRY (STN), CA (STN), CAOLD (STN), CAI		rch terms used)
C. DOCUI	MENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where ap	<u> </u>	Relevant to claim No.
X A	Khalid, M. et al., "N,N'-disubs as novel cancer chemotherapeutic; Res., Vol.13, Suppl.1, pp.57-60	agents", Drugs Exp. Clin.	1-3,9-11 4-8
X A	WO, 98/50534, Al (SMITHKLINE BE 12 November, 1998 (12.11.98) & EP, 991753, Al & AU, 98728 & ZA, 9803843, A & NO, 99054		1-3,9-11 4-8
X A	EP, 217286, A1 (OKAMOTO, SHOSUK 08 April, 1987 (08.04.87), compounds No.42 & JP, 63-022061, A & US, 48958 & CA, 1297633, A & AU, 63051	842, A	11 1-10
PX	WO, 99/25686, A1 (TEIJIN LIMITE 27 May, 1999 (27.05.99) & AU, 9913741, A	ED),	1-11
PX	WO, 00/31032, A1 (F.HOFFMANN-LA 02 June, 2000 (02.06.00), & DE, 19955794, A	ROCHE AG),	1-11
	r documents are listed in the continuation of Box C.	See patent family annex.	
Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance earlier document but published on or after the international filing		"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be	
date "L" docume	ent which may throw doubts on priority claim(s) or which is establish the publication date of another citation or other	considered novel or cannot be consider step when the document is taken alone "Y" document of particular relevance; the c	red to involve an inventive
special "O" docume	reason (as specified) ent referring to an oral disclosure, use, exhibition or other	considered to involve an inventive step combined with one or more other such	when the document is documents, such
	ent published prior to the international filing date but later priority date claimed	"&" document member of the same patent f	
	ictual completion of the international search august, 2000 (09.08.00)	Date of mailing of the international scare 22 August, 2000 (22.	
Name and mailing address of the ISA/ Japanese Patent Office		Authorized officer	
Facsimile No.		Telephone No.	

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP00/03203

tegory*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
1	GB, 2343893, A & FR, 2786185, A	
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with initiation, progression and maintenance of diseases wherein monocytes, lymphocytes and the like are assumed to be deeply associated with the progression of lesion, for example, atherosclerosis, rheumatoid arthritis, psoriasis, asthma, ulcerative colitis, nephritis (nephropathy), multiple sclerosis, pulmonary fibrosis, myocarditis, hepatitis, pancreatitis, sarcoidosis, Crohn's disease, endometriosis, congestive heart failure, viral meningitis, cerebral infarction, neuropathy, Kawasaki disease and sepsis (see, for example, Rovin, B. H. et al., Am. J. Kidney. Dis., 1998, 31, 1065; Lloyd, C. et al., Curr. Opin. Nephrol. Hypertens., 1998, 7, 281; Conti, P. et al., Allergy and Asthma Proc., 1998, 19, 121; Ransohoff, R. M. et al., Trends Neuroscience., 1998, 21, 154; and MacDermott, R. P. et al., Inflammatory Bowel Diseases, 1998, 4, 54). A drug which inhibits actions of chemokines on target cells, therefore, can be expected to be useful as remedies and/or prophylactics for the diseases.

[0013] On the other hand, the cloning of genes encoding specific receptors for chemokines has been promoted, and it has become apparent that the receptors are G protein-coupled seven-transmembrane receptors present on various leukocytes. At least 5 CXC chemokine receptors (CXCR1 to CXCR5) and eight CC chemokine receptors (CCR1 to CCR8) have hitherto been specified. For example, IL-8 is a ligand of CXCR1 and CXCR2. MIP-1α is a ligand of CCR1 and CCR5, and MCP-1 is a ligand of CCR2A and CCR2B (see, for example, Holmes, W. E. et al., Science, 1991, 253, 1278-1280; Murphy, P. M. et al., Science, 253, 1280-1283; Neote, K. et al., Cell, 1993, 72, 415-425; Charo, I. F. et al., Proc. Natl. Acad. Sci., USA, 1994, 91, 2752-2756; Yamagami, S. et al., Biochem. Biophys. Res. Commun., 1994, 202, 1156-1162; Combadier, C. et al., The Journal of Biological Chemistry, 1995, 270, 16491-16494; Power, C. A. et al., J. Biol. Chem., 1995, 270, 19495-19500; Samson, M. et al., Biohemistry, 1996, 35, 3362-3367; and Murphy, P. M. et al., Annual Review of Immunology, 1994, 12, 592-633).

[0014] Further, it has been reported that the pulmonary inflammation and granuloma are suppressed in CCR1 gene deficient mice (see, for example, Gao, J.-L. et al., J. Exp. Med., 1997, 185, 1959 and Gerard, C. et al., J. Clin. Invest., 1997, 100, 2022) and that accumulation of macrophages and formation of atherosclerotic lesions are decreased in CCR2 gene deficient mice (see, for example, Boring, L. et al., Nature, 1998, 394, 894; Kuziel, W. A. et al., Proc. Natl. Acad. Sci. USA, 1997, 94, 12053; Kurihara, T. et al., J. Exp. Med., 1997, 186, 1757; and Boring, L. et al., J. Clin. Invest., 1997, 100, 2552). Therefore, compounds capable of inhibiting binding of chemokines such as MIP-1 α and/or MCP-1 to the receptors, i.e. chemokine receptor antagonists can be expected to be useful as a drug which inhibits the actions of the chemokines such as MIP-1 α and/or MCP-1 on target cells; however, the drug having the actions is not known. [0015] Cyclic amine derivatives such as various kinds of piperidines or piperazines have recently been reported to have chemokine receptor antagonistic activity (see, for example, WO9724325; Hesselgesser, J. et al., J. Biol. Chem., 1998, 273, 15687; Howard, O. M. Z. et al., J. Med. Chem., 1998, 41, 2184; WO9744329; WO9802151; WO9804554; WO9825605; WO9825617; WO9825604; WO9831364; WO9856771; WO9909984; WO9904794; WO9917773; WO9937619; WO9937651; WO9938514; WO200014086; WO200014089; EP903349; JP9-249566; JP9-25572; and JP11-711350). The compounds, however, are different from the compounds used in the present invention.

Disclosure of the Invention

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[0016] It is an object of the present invention to provide therapies for diseases wherein the binding of chemokines such as MIP-1 α and/or MCP-1 to receptors on target cells is one of the pathogenesis by using a small-molecular compound having an inhibitory activity against the binding of the chemokines such as MIP-1 α and/or MCP-1 to the receptors on the target cells.

[0017] As a result of intensive studies, the present inventors have found that cyclic amine derivatives having an arylalkyl group, pharmaceutically acceptable C_1 - C_6 alkyl-addition salts thereof or pharmaceutically acceptable acid-addition salts thereof have an inhibitory activity against the binding of chemokines such as MIP-1 α and/or MCP-1 to the target cells and that the compounds can be useful as remedies or prophylactics for diseases considered to be associated with the chemokines such as MIP-1 α and/or MCP-1. The present invention has been accomplished on the basis of the findings.

[0018] That is, the present invention is remedies or prophylactics for diseases in association with chemokines or chemokine receptors comprising compounds represented by the following formula (I), pharmaceutically acceptable acid addition salts thereof or pharmaceutically acceptable C_1 - C_6 alkyl addition salts thereof as an active ingredient,

$$\begin{array}{c}
R^{1} \\
(CH_{2})_{i} - N \\
(CH_{2})_{m}
\end{array}$$

$$\begin{array}{c}
(CH_{2})_{n} - N - C \\
(CH_{2})_{m}
\end{array}$$

$$\begin{array}{c}
(CH_{2})_{p} + R^{4} \\
(CH_{2})_{p} + R^{5}
\end{array}$$

$$\begin{array}{c}
(CH_{2})_{q} - G - R^{6} \\
(I)
\end{array}$$

$$\begin{array}{c}
(I) \\
(CH_{2})_{m}
\end{array}$$

$$\begin{array}{c}
(I) \\
($$

the acid include a mineral acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid or carbonic acid and an organic acid such as maleic acid, citric acid, malic acid, tartaric acid, fumanic acid, methanesulfonic acid, trifluoroacetic acid or formic acid.

[0096] Furthermore, C₁-C₆ alkyl addition salts of the cyclic amine compounds, for example, 1-(4-chlorobenzyl)-1-methyl4-[{N-(3-trifluoromethylbenzoyl)glycyl}aminomethyl]piperidinium iodide are also used in the present invention. The alkyl group preferably includes methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, tert-pentyl, 2-methylpentyl and 1-ethylbutyl herein; however, methyl group, ethyl group or the like is especially preferable. A halide anion such as fluoride, chloride, bromide or iodide is preferable for a counter anion of an ammonium cation.

[0097] In the present invention, a racemate and all the possible optically active forms of the compounds represented by the above formula (I) can also be used.

[0098] The compounds represented by the above formula (I) can be synthesized by using any of the following general preparation processes described in WO9925686:

(Preparation process 1)

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[0099] A preparation process comprises reacting one equivalent of a compound represented by the following formula (II):

wherein R^1 , R^2 , R^3 , j, k, m and n are each the same as defined in the above formula (I), with 0.1 to 10 equivalents of a carboxylic acid represented by the following formula (III):

$$\begin{array}{c} O \\ HO - C - (CH_2)_p - \frac{R^4}{R^5} (CH_2)_q - G - R^6 \end{array}$$
 (III)

wherein R^4 , R^5 , R^6 , G, p and q are each the same as defined in the above formula (I), or a reactive derivative thereof in the absence or presence of a solvent.

[0100] The "reactive derivative" of the carboxylic acid represented by the above formula (III) mean a carboxylic acid derivative, for example, an acid halide, an acid anhydride or a mixed acid anhydride usually used in the synthetic organic chemistry field and having high reactivity.

[0101] The reaction can more smoothly be made to proceed by suitably using an adequate amount of a dehydrating agent such as molecular sieve; a coupling reagent such as dicyclohexylcarbodiimide (DCC), N-ethyl-N'-(3-dimethylaminopropyl)carbodilmide (EDCI or WSC), carbonyldiimidazole (CDI), N-hydroxysuccinimide (HOSu), N-hydroxybenzotriazole (HOBt), benzotriazol-1-yloxytris(pyrrolidinol) phosphonium hexafluorophosphate (PyBOP), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-(5-norbornene-2,3-dicarboxyimide)-1,1,3,3-tetramethyluronium tetrafluorobonite (TNTU), O-(N-succinimidyl)-1,1,3,3-tetramethyluronium hexafluorophosphate (TSTU) or bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP); a base such as an inorganic base such as potassium carbonate, calcium carbonate or sodium hydrogencarbonate; aprines such as triethylamine, diisoproylethylamine or pyridine or a polymer supported base such as (piperidinomethyl)polystyrene, (morpholinomethyl)polystyrene, (dimethylaminomethyl)polystyrene or poly(4-vinylpyridine).

(Preparation process 2)

[0102] A preparation process comprises reacting one equivalent of an alkylating reagent represented by the following formula (IV):

$$\begin{array}{c}
R^1 \\
 \longrightarrow (CH_2)_j -X
\end{array} (IV)$$

wherein R^1 , R^2 and j are each the same as defined in the above formula (I); X is a halogen atom, an alkylsulfonyloxy group or an arylsulfonyloxy group, with 0.1 to 10 equivalents of a compound represented by the following formula (V):=

$$\begin{array}{c} \begin{pmatrix} (CH_{2})_{k} \\ HN \\ (CH_{2})_{m} \end{pmatrix} - (CH_{2})_{n} - N - C \\ R^{3} \\ \end{pmatrix} - (CH_{2})_{p} - R^{4} \\ (CH_{2})_{q} - G - R^{6} \\ \end{array}$$
 (V)

wherein R³, R⁴, R⁵, R⁶, G, k, m, n, p and q are each the same as defined in the above formula (I), in the absence or presence of a solvent.

[0103] The reaction can more smoothly be made to proceed by suitably using a base similar to that in the preparation process 1. Furthermore, the reaction sometimes can be promoted by the presence of an iodide such as potassium iodide or sodium iodide.

[0104] In the above formula (IV), X is a halogen atom, an alkylsulfonyloxy group or an arylsulfonyloxy group. Examples of the halogen atom preferably include a chlorine atom, a bromine atom and an iodine atom. Specific examples of the alkylsulfonyloxy group preferably include a methylsulfonyloxy group, a trifluoromethylsulfonyloxy group and the like, and the specific example of the arylsulfonyloxy group preferably includes tosyloxy group.

(Preparation process 3)

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30 [0105] A preparation process comprises reacting one equivalent of an aldehyde represented by the following formula (VI):

$$R^1$$
 (CH₂)_{j-1}-CHO (VI)

wherein R^1 and R^2 are each the same as defined in the above formula (I); j is 1 or 2, or an aldehyde represented by the following formula (VII):

wherein R¹ is the same as defined for R¹ in the above formula (I); the compound corresponds to the case where j is 0, with 0.1 to 10 equivalents of a compound represented by the above formula (V) in the absence or presence of a solvent.
 [0106] The reaction is usually called a reductive amination reaction and a catalytic hydrogenation reaction using a catalyst containing a metal such as palladium, platinum, nickel or rhodium, a hydrogenation reaction using a complex hydride such as lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride and borane, an electrolytic reducing reaction or the like can be used as reductive conditions.

(Preparation process 4)

[0107] A preparation process comprises reacting one equivalent of a compound represented by the following formula (VIII):

wherein R¹, R², R³, R⁴, R⁵, R⁷, j, k, m, n, p and q are each the same as defined in the above formula (I), with 0.1 to 10 equivalents of a carboxylic acid or a sulfonic acid represented by the following formula (IX):

wherein R⁶ is the same as defined in the above formula (I); A is a carbonyl group or a sulfonyl group, or a reactive derivative thereof in the absence or presence of a solvent

[0108] The reactive derivative of the carboxylic acid or sulfonic acid represented by the above formula (IX) means a carboxylic acid derivative or sulfonic acid derivative, for example, an acid halide, an acid anhydride or a mixed acid anhydride usually used in the synthetic organic chemistry field and having high reactivity. The reaction can more smoothly be made to proceed by suitably using a dehydrating agent, a coupling reagent or a base similar to that in the above preparation process 1.

(Preparation process 5)

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[0109] A preparation process comprises reacting one equivalent of a compound represented by the above formula (VIII) with 0.1 to 10 equivalents of an isocyanate or an isothiocyanate represented by the following formula (X):

$$Z=C=N-R^{6}$$
 (X)

wherein R^6 is the same as defined in the above formula (I); Z is an oxygen atom or a sulfur atom, in the absence or presence of a solvent.

(Preparation process 6)

[0110] A preparation process comprises reacting one equivalent of a compound represented by the following formula (XI):

wherein R¹, R², R³, R⁴, R⁵, j, k, m, n, p and q are each the same as defined in the above formula (i); A is a carbonyl group or a sulfonyl group,

with 0.1 to 10 equivalents of an amine represented by the following formula (XII):

$$R^6-NH_2$$
 (XII)

wherein R⁶ is the same as defined for R⁶ in the above formula (I), in the absence or presence of a solvent.

[0111] The reaction can more smoothly be made to proceed by suitably using a dehydrating agent, a coupling reagent or a base similar to that in the above preparation process 1.

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deprotest.

[0112] In the above preparation processes 1 to 6, when a substrate used for each reaction has substitutents regarded as usually reacting under respective reaction conditions in the organic synthetic chemistry or having adverse effects on the reaction, the functional groups can be protected with a known suitable protecting group, and the substrate can be used for the reaction and then deprotected by a conventional known method to afford the objective compound.

[0113] In addition, the compounds used in the present invention can be obtained by further converting (single or plural) substituents of the compound produced by the above preparation process 1 - 6 using a known reaction usually used in the organic synthetic chemistry, for example, an alkylation reaction, an acylation reaction or a reduction reaction. [0114] In the above respective preparation processes, a halogenated hydrocarbon such as dichloromethane or chloroform, an aromatic hydrocarbon such as benzene or toluene, ethers such as diethyl ether or tetrahydrofuran, esters such as ethyl acetate, an aprotic polar solvent such as dimethylformamide, dimethyl sulfoxide or acetonitrile and alcohols such as methanol, ethanol or isopropyl alcohol are suitably used as a reaction solvent according to the reaction. [0115] In each of the preparation processes, the reaction temperature is within the range of -78 to +150 °C, preferably within the range of 0 to 100°C. After completing the reaction, the objective cyclic amine compounds represented by the above formula (I) can be isolated by carrying out usual isolating and purifying operations, i.e., concentration, filteration, extraction, solid-phase extraction, recrystallization or chromatography. The compounds can be converted into their pharmaceutically acceptable acid addition salts thereof or their C_1 - C_6 alkyl addition salts thereof according to a usual method.

Examples

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[0116] The present invention is detailed specifically based on Examples; however, the present invention is not restricted to compounds described in the Examples. The Compound number (Compd. No.) assigned to each compound in the following Examples corresponds to the Compd. No. assigned to each compound cited as a preferred specific example in Tables 1.1 to 1.206.

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[Reference Example 1] Synthesis of 3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride

[0117] 4-Chlorobenzyl chloride (4.15 g, 25.8 mmol) and $^{1}\text{Pr}_{2}\text{NEt}$ (6.67 g, 51.6 mmol) were added to a DMF (50 mL) solution of 3-[(tert-butoxycarbonyl)amino]pyrrolidine (4.81 g, 25.8 mmol). The reaction mixture was stirred at 70 °C for 15 hours, and the solvent was removed under reduced pressure. The objective 3-[(tert-butoxycarbonyl)amino]-1-(4-chlorobenzyl)pyrrolidine (6.43 g, 80%) was obtained as an off-white solid by recrystallization (acetonitrile, 50 mL). ^{1}H NMR (CDCl₃, 300MHz) δ 1.37 (s, 9 H), 1.5-1.7 (br, 1 H), 2.1-2.4 (m, 2 H), 2.5-2.7 (m, 2 H), 2.83 (br, 1 H), 3.57 (s, 2 H), 4.1-4.3 (br, 1 H), 4.9-5.1 (br, 1 H), 7.15-7.35 (br, 4 H); the purity was determined by RPLC/MS (98%). ESI/MS m/e 311.0 (M⁺+H, C₁₆H₂₄ClN₂O₂).

[0118] To a methanol solution (80 mL) of the 3-[(tert-butoxycarbonyl)amino]-1-(4-chlorobenzyl)pyrrolidine (6.38 g, 20.5 mmol), was added 1 M HCl-Et₂O (100 mL). The resulting mixture was stirred at 25 °C for 15 hours. The solvent was removed under reduced pressure to provide a solid, which was purified by recrystallization (methanol/acetonitrile = 1:2, 130 mL) to thereby afford 3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride (4.939 g, 85%) as a white powder. ¹H NMR (d₈-DMSO, 300MHz) δ 3.15 (br, 1 H), 3.3-3.75 (br-m, 4 H), 3.9 (br, 1 H), 4.05 (br, 1 H), 4.44 (br, 1 H), 4.54 (br, 1 H), 7.5-7.7 (m, 4 H), 8.45 (br, 1 H), 8.60 (br, 1 H); the purity was determined by RPLC/MS (>99%). ESI/MS m/e 211.0 (M*+H, C₁₁H₁₆ClN₂).

[0119] Optically active (R)-3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride and (S)-3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride were synthesized by using the respective corresponding starting materials according to the above method. The products exhibited the same ¹H NMR as that of the above racemate.

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[Example 1] Synthesis of 3-(N-benzoylglycyl)amino-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 1)

[0120] N-Benzoylglycine (9.3 mg, 0.055 mmol), 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (ED-CI) (1.05 mg) and 1-hydroxybenzotriazole hydrate (HOBt) (7.4 mg) were added to a chloroform (2.5 mL) solution of 3-amino-1-(4-chlorobenzyl)pyrrolidine dihydrochloride (14.2 mg, 0.050 mmol) and triethylamine (15.2 mg). The resulting reaction mixture was stirred at 25 °C for 16 hours and then washed with a 2 M aqueous solution of NaOH (2mL \times 2) and brine. After filtration through a PTFE membrane filter, the solvent was removed under reduced pressure to provide 3-(N-benzoylglycyl)amino-1-(4-chlorobenzyl)pyrrolidine (Compd. No. 1) as an off-white oil (17.7 mg, 95%). The purity was determined by RPLC/MS (95%). ESI/MS mle 372.0 (M*+H, $C_{20}H_{22}CIN_3O_2$).

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[Examples 2 to 32]

[0121] The compounds used in the present invention were synthesized by using the respective corresponding starting